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TUMORS OF THE PARATHYROID GLANDS

Benjamin Castleman, M. D.

ARMED FORCES INSTITUTE OF PATHOLOGY

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ATLAS OF TUMOR PATHOLOGY

Section IV—Fascicle 15

TUMORS OF THE PARATHYROID GLANDS

by
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Benjamin Castleman

TUMORS OF THE PARATHYROID GLANDS

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TUMORS OF THE PARATHYROID GLANDS

INTRODUCTION

The word "tumor" in the title of this fascicle is used literally to mean a swelling or enlargement, because some of the conditions to be discussed are not true neoplasms, but lesions that must be differentiated from the true neoplasms. Enlargement of the parathyroid glands may be classified in many ways, but I have chosen the functional basis:

Primary hyperparathyroidism
- Adenoma, single or multiple.
- Carcinoma, primary.
- Primary hyperplasia and hypertrophy involving all four glands.

Secondary hyperparathyroidism
- Hyperplasia involving all four glands.

Nonfunctional enlargements
- Oxyphil "adenomas."
- Cysts.
- Carcinoma:
  - Primary.
  - Metastatic.

Normal Parathyroid Gland

In order to recognize the lesions listed above, it is necessary to know the variations of the gross and microscopic appearance of the normal gland.

The normal adult gland measures 3 to 6 mm. in length, 2 to 4 mm. in width, and 0.5 to 2 mm. in thickness. Each gland weighs usually between 30 and 35 mg., so that the combined weight of the four glands is between 120 and 140 mg. Gilmour and Martin in their exhaustive study of the weights of the parathyroid glands showed that the two lower glands are slightly heavier than the upper, and that the glands in females are slightly heavier than in males. (For location of the normal parathyroid glands see discussion under Adenoma, p. 24.)

Microscopically, a large part of the normal gland of most adults is composed of large groups of fat cells. These appear following puberty and increase in number until about 40 years of age (fig. 1). During middle age the fat tissue remains fairly constant and often decreases in amount in elderly individuals.

For all practical purposes there are really two types of cells: the chief cell and the pale oxyphil cell, which is believed to be an involuted chief cell. The

NORMAL PARATHYROID GLAND

Figure 1. Cross section of an entire gland showing average number of fat cells in a middle-aged individual. A. F. I. P. Acc. No. 218954–80.

Figure 2. Chief cells separated by fat cells. An occasional cell shows some vacuolization of the cytoplasm. × 400. A. F. I. P. Acc. No. 218954–52.

Fig. 1

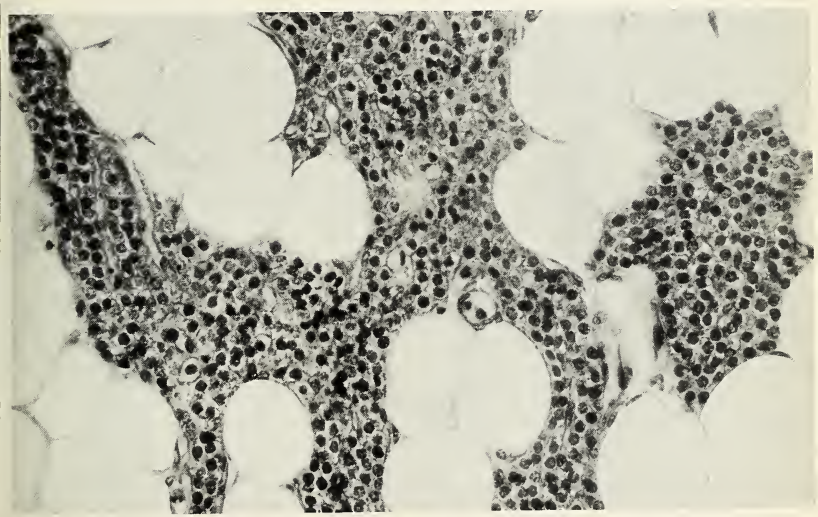

Fig. 2

NORMAL PARATHYROID GLAND

Figure 3. Cross section of an entire gland from an elderly individual showing a large island of oxyphil cells and many smaller islands amid the chief cells. × 25. A. F. I. P. Acc. No. 218954–78.

Figure 4. Higher power of one of the smaller oxyphil islands in figure 3. × 165. A. F. I. P. Acc. No. 218954–76.

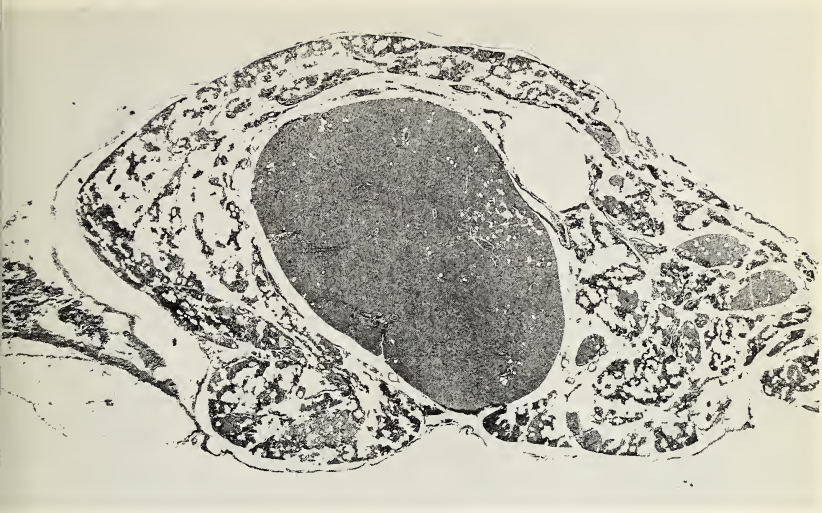

Fig. 3

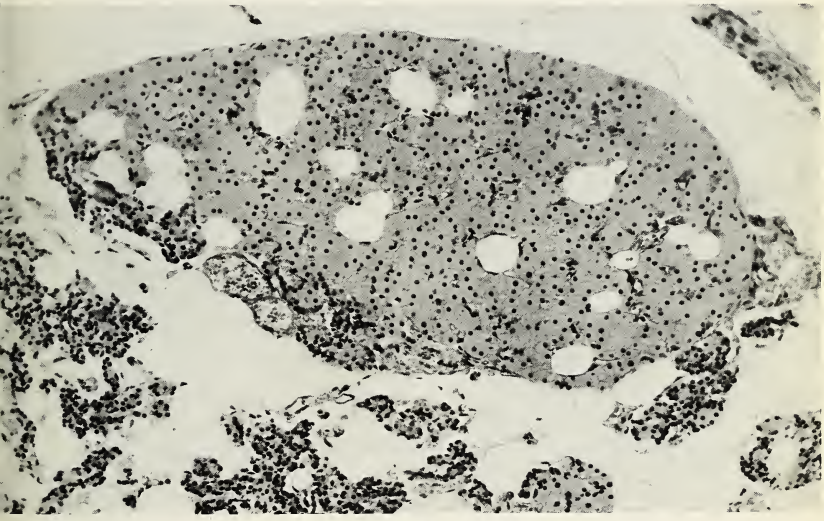

Fig. 4

other types often mentioned such as the "wasserhelle" cell and the dark oxyphil cell are probably also modifications of the chief cell.

The detailed description of these cells (figs. 2–4) may be quoted from Castleman and Mallory (1935):

"The normal chief or principal cell . . . is polyhedral in shape, poorly outlined, and measures 6–8 microns in diameter. Its nucleus is large, round, sharply demarcated by a basophilic outline, comprises more than half of the cell volume, and measures 4–5 microns in diameter. The chromatin is usually abundant, often giving the nucleus a pyknotic appearance. The cytoplasm is usually very scant and faintly acidophilic. Often it is more or less retracted toward the cell margins, leaving an unstained halo of varying width about the nucleus. This is often spoken of as vacuolization, though it may represent merely an artifact of fixation and dehydration. Formalin fixation tends to exaggerate this appearance, and in frozen sections of unfixed tissue vacuolization is difficult to demonstrate even when paraffin sections show it in marked form. Cells showing this halo formation in moderate degree we have termed transition wasserhelle cells.

"When the cytoplasm is apparently entirely absent, complete vacuolization, the cell is called a 'water-clear' or 'wasserhelle' cell. At this stage the cell is sharply outlined and is larger than the chief cell, measuring 10–15 microns in diameter. Its nucleus is about the same size as that of the chief cell, but is usually more hyperchromatic, more often pyknotic, and eccentrically located. These cells are seen only occasionally in the apparently normal gland and then in small groups. We have not observed them before puberty. Their presence in small clusters has sometimes been interpreted as focal hyperplasia. When the whole gland is composed of these cells, as in some cases of nephritis and hypertension, it is felt that hyperplasia is definite.

"The pale oxyphil cell . . . is polyhedral in shape, has a sharply demarcated cell margin and measures 11–14 microns in diameter. The nucleus is also about the same size as that of the chief cell, but not so hyperchromatic. The cytoplasm is uniformly reddish pink, finely granular and completely fills the cell. . . .

". . . At puberty or soon afterward pale oxyphils gradually appear, at first singly and then in pairs. They increase in number with advancing age, forming large islands usually after forty to fifty years of age. . . . These islands are sharply circumscribed but not encapsulated, and often continuous cords of parenchymal cells can be traced across the margin into the surrounding tissue."*

*Castleman, B., and Mallory, T. B. The pathology of the parathyroid gland in hyperparathyroidism. A study of 25 cases. Am. J. Path., 11: 1–72, 1935.

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Castleman, B., and Mallory, T. B. The pathology of the parathyroid gland in hyperparathyroidism. A study of 25 cases. Am. J. Path., 11: 1–72, 1935.

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Welsh, D. A. Concerning the parathyroid glands: a critical, anatomical and experimental study. J. Anat. & Physiol., 32: 380–402, 1898.

Plate I. Parathyroid Adenomas

A. The tumor is partially embedded in fat. Note the characteristic orange-brown color. A. F. I. P. Acc. No. 218954–91.

B. External and sectional views of a large tumor weighing 3 gm. Note the marked cystic and hemorrhagic degeneration. A. F. I. P. Acc. No. 218954–94.

C. A very large tumor weighing over 50 gm. Note the yellowish plaques of calcification in the capsule. A. F. I. P. Acc. No. 218954–92.

D. The cut surface of the preceding tumor. When cut, a large amount of turbid fluid exuded, producing collapse of the tumor. Note the numerous septa which are the result of the cystic degeneration. The linear white area in the center is a part of the inner aspect of the capsule that has separated from the tumor. A. F. I. P. Acc. No. 218954–93.

A

B

C

D

Plate I

PRIMARY HYPERPARATHYROIDISM

The observations recorded in this section are based on material removed from over 100 patients with primary hyperparathyroidism at the Massachusetts General Hospital.

Clinical Features

There are three main clinical types: (1) The so-called "classic" type which corresponds to what was originally described by von Recklinghausen in 1891 as osteitis fibrosa cystica generalisata. (He was unaware of the relation of this bone disease to the parathyroid gland.) In this type there is generalized decalcification with the formation of bone cysts, "brown tumors," multiple fractures, and elevated serum alkaline phosphatase (figs. 5–8). There may or may not be renal stones. (2) The type characterized by generalized mild osteoporosis without any cysts or tumors, but usually with renal stones. (3) The type in which there are no bone changes but only renal stones.

In all three types there is an elevated serum calcium and a lowered serum phosphorus. The increased excretion of calcium through the kidneys produces precipitation in the tubules with subsequent diffuse renal calcinosis with or without stone formation (figs. 9-12). The third type, namely that without bone changes, accounts for more than half the cases of primary hyperparathyroidism, so that serum calcium and phosphorus determinations are mandatory in all cases of nephrolithiasis, especially where the stones are bilateral. About 5 percent of all renal stones are associated with hyperparathyroidism.

The youngest patient was 12 years of age, the oldest 72; 80 percent of the patients were between 30 and 60 years of age. The age distribution was the same among the various clinical and anatomical types of primary hyperparathyroidism. Females predominated in a ratio of 7 to 3, except that in the 10 cases of primary hyperplasia and hypertrophy, the sexes were equally divided.

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Albright, F. and Reifenstien, E.C., Jr. The parathyroid glands and metabolic bone disease; selected studies. Baltimore: Williams & Wilkins, 1948.

von Recklinghausen, F. Die fibröse oder deformirende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen. In: Festschrift Rudolph Virchow zu seinem 71. Geburtstage. Berlin: G. Reimer, 1891.

OSTEITIS FIBROSA CYSTICA GENERALISATA

Figure 5. All three manifestations of the disease are present. On the right is the extreme fibrosis between bone trabeculae; in the upper portion are three cysts, and in the rest of the section are islands of giant cells (osteoclasts) with hemorrhage—the so-called "brown tumor." × 12. A. F. I. P. Acc. No. 218954–96.

Figure 6. A higher magnification of one of the "brown tumors" showing the hemorrhage between the osteoclasts. It is degeneration of these areas that leads to cyst formation. × 100. A. F. I. P. Acc. No. 218954–97.

Figure 7. A characteristic roentgenogram showing generalized decalcification with two cysts in a femur. A. F. I. P. Acc. No. 218954–98.

Fig. 5

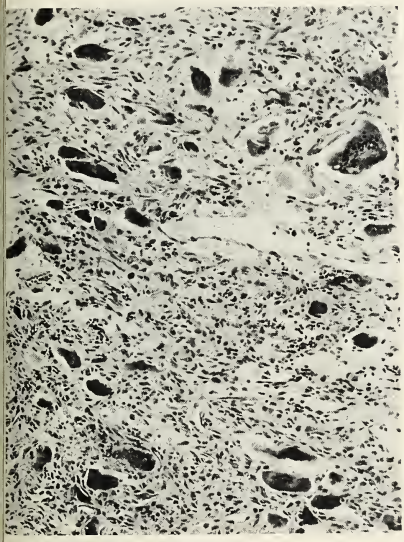


Fig. 6

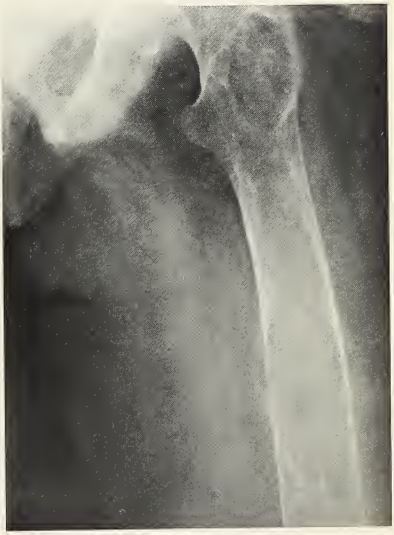


Fig. 7

OSTEITIS FIBROSA CYSTICA GENERALISATA

Figure 8. A series of tibial biopsies removed from the same patient at different intervals:

A. At the time of removal of a parathyroid adenoma. Note the extensive bone resorption characterized by the irregularity of the surfaces of the trabeculae producing Howship's lacunae, and the large numbers of osteoclasts. Note also the line of osteoblasts on other bone surfaces. × 100. A. F. I. P. Acc. No. 218954–99.

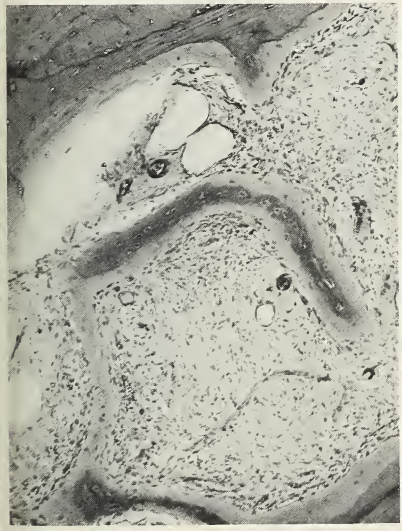
B. One week after removal of adenoma. The osteoclasts are gone. Osteoblasts line all the trabeculae and osteoid is making its appearance. × 100. A. F. I. P. Acc. No. 218954–100.

C. Five weeks after removal of adenoma. Much more osteoid is present and the fibrous tissue is beginning to be replaced by fat cells. × 100. A. F. I. P. Acc. No. 218954–101.

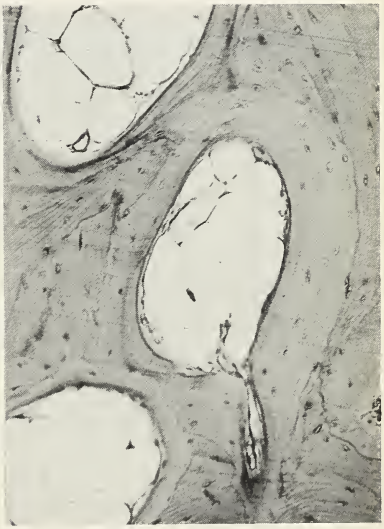
D. Four months after removal of adenoma. The bone is almost normal. × 100. A. F. I. P. Acc. No. 218954–102.

A

B



C



D

Fig. 8

RENAL CALCINOSIS

Figure 9. Plain abdominal roentgenogram showing the distribution of the calcification in the renal tubules in a case of primary hyperparathyroidism produced by a parathyroid adenoma. Most cases, especially those without bone disease, show only renal stones and not such extensive calcinosis. A. F. I. P. Acc. No. 218954–107.

Figure 10. Roentgenogram of a pair of kidneys with calcinosis, obtained at autopsy three years after removal of a parathyroid adenoma. Irreversible renal damage had apparently been present before operation. A. F. I. P. Acc. No. 218954–108.

Fig. 9

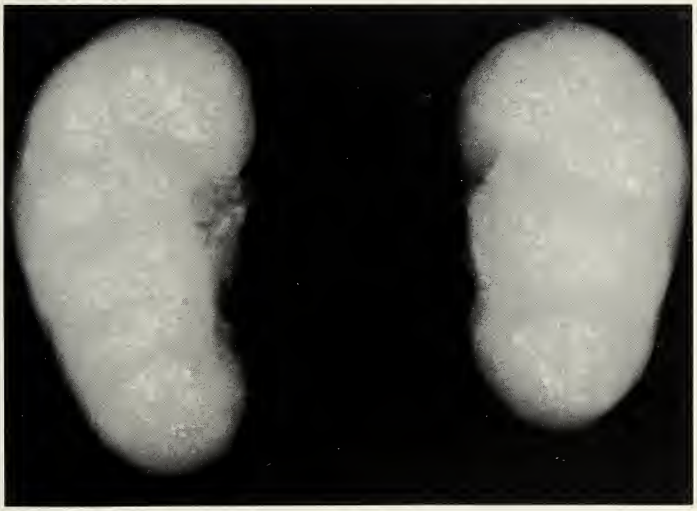


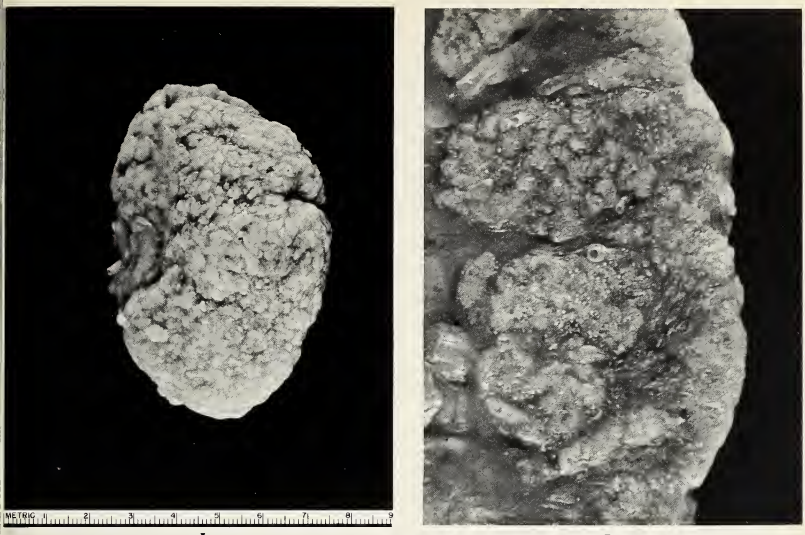
Fig. 10

RENAL CALCINOSIS

Figure 11.* A and B: External and cross section of kidney, showing extensive calcification, which appears in the illustration as white spots but which were yellow spots in the natural color. The patient had a parathyroid adenoma and died of renal insufficiency. A. F. I. P. Acc. No. 218954–103 and 104.

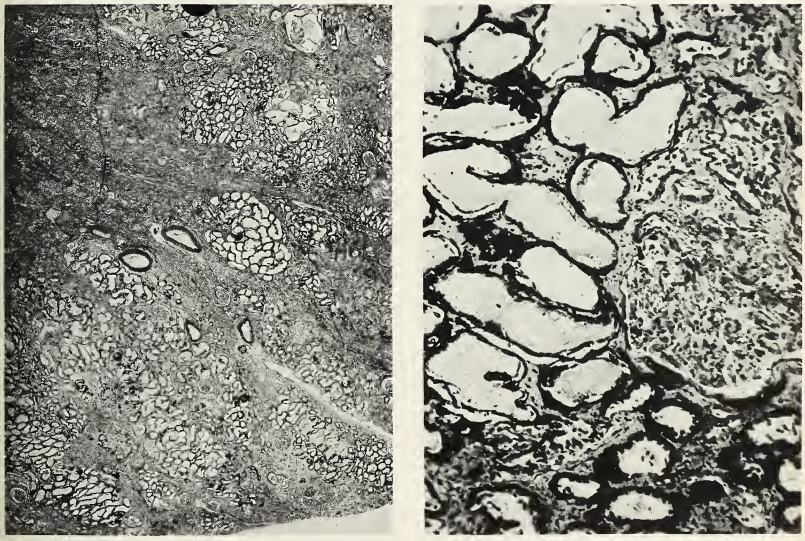
Figure 12.* A and B: Von Kossa stain of kidney of same case showing extensive calcification of parenchyma, especially in wall of tubules. A. F. I. P. Acc. No. 218954–105 and 106.

* Illustrated by courtesy of Dr. Edward A. Gall, Cincinnati, Ohio.



A B

Fig. 11



A B

Fig. 12

Adenoma

Adenoma of the parathyroid gland is by far the most common cause of primary hyperparathyroidism, being responsible for 89 percent of the first 100 cases of the Massachusetts General Hospital series; the other 11 percent were caused by primary hyperplasia and hypertrophy and by carcinoma.

The location of the adenoma obviously depends upon the site of the normal parathyroid. The latter, however, may occur in abnormal anatomical positions that may be explained embryologically. The upper parathyroid glands develop in association with the anlage of the thyroid gland from the fourth branchial pouches and normally descend as far as the level of the cricoid cartilage on either side to the posterolateral or inner surface of the lateral lobes of the thyroid gland. Occasionally, there may be slight invagination of the parathyroid gland into the capsule of the thyroid gland so that it may appear as if the parathyroid is really within the thyroid.

The lower parathyroid glands, which develop from the third branchial pouch along with the thymus gland, usually are more aberrant in location than are the upper glands. These glands normally descend to the lower border of the thyroid gland. In some instances, however, they do not stop at this point but migrate with the thymus into the anterior mediastinum (fig.13). Such migration explains the mediastinal position of about 20 percent of the adenomas observed at the Massachusetts General Hospital (fig.14). Assuming that the mediastinal tumors originate in the lower glands, then approximately 75 percent of the adenomas develop in the lower glands and 25 percent in the upper glands; there is no preponderance of one side over the other. The incidence of adenomas in the lower glands is even higher in the cases reported in the literature. One should bear in mind, however, that some of the large tumors that involve an upper gland may have descended into the superior mediastinum because of size alone, and so appear in the position of or even below the lower glands.

The usual blood supply to both upper and lower parathyroid glands is from branches of the inferior thyroid artery. In a fair proportion of cases a parathyroid gland is supplied by a branch of the superior thyroid artery. Embryologically, this gland is probably the upper parathyroid gland (IV) and may have descended to an anatomical position below the true lower gland (III). If the surgeon carefully dissects the blood supply of the gland and follows it back to its source, it may help him to decide whether a gland is upper or lower.

The adenoma may involve only a part of a gland and thus remain fairly small, sometimes weighing less than 0.1 gm.(figs. 18 , 19). More often it replaces the entire gland, so that no rim of normal parenchyma is seen. Occasionally an adenoma may be palpated in the neck but more often palpable nodules prove to be thyroid tissue.

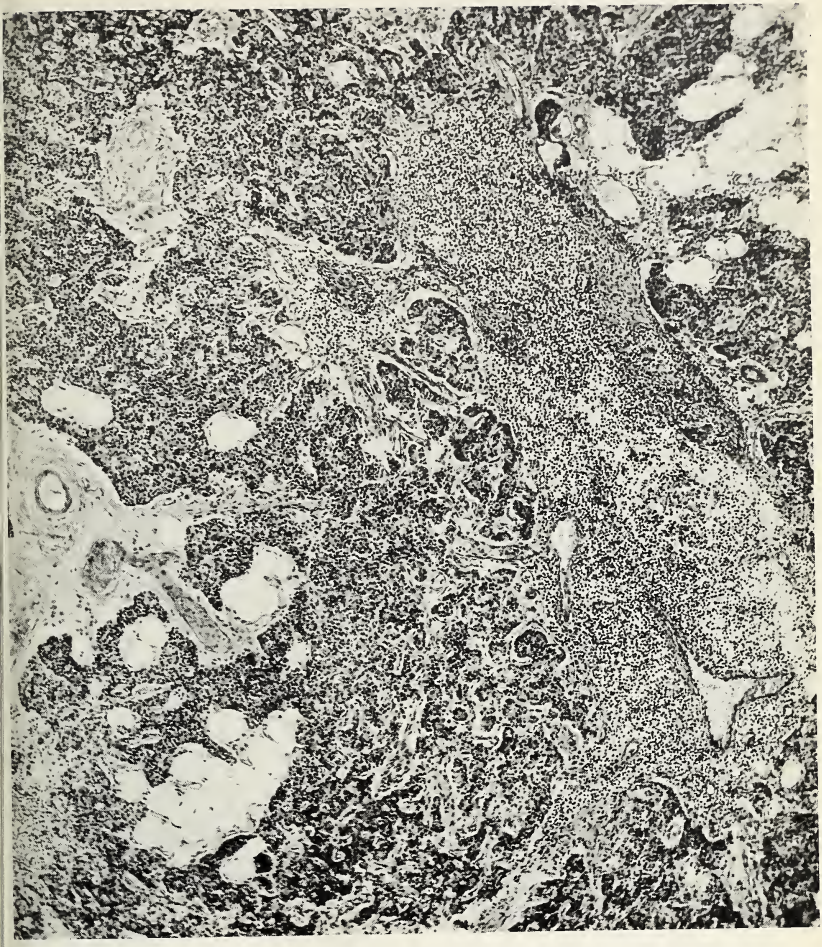


Figure 13. Normal parathyroid tissue within thymic tissue. × 100. A. F. I. P. Acc. No. 218954–71.

In six of our cases an adenoma was found in two glands. In four of these patients both adenomas were observed at the first operation, while in two of these patients, the second adenoma was removed at a subsequent operation five and nine years later respectively.

The larger adenomas occur in the classic type of the disease; in this group the average weight was 9.4 gm. with the largest weighing 53 gm. (fig. 15). In sharp contrast, the average weight in the nonclassic cases was 1.3 gm., with the great majority under 1 gm. (fig. 16).

An interesting observation was the finding of a rough correlation of the level of blood serum calcium with size of the tumor: the higher the calcium level, the larger the tumor. This agrees with the fact that the average serum calcium was 14.3 mg. per 100 cc. in the classic cases and 12.4 mg. per 100 cc. in the nonclassic cases (fig. 17).

GROSS. The usual adenoma is an encapsulated orange-brown, soft, somewhat pliable, occasionally lobular mass embedded in fat tissue (pl. I–A). This soft orange-brown tissue is quite different from the pink-to-red firmer thyroid tissue and from the pink or yellow-pink, better defined, less pliable lymph node—the two tissues that are often mistaken for parathyroid gland. Its shape is variable: When small, it is more like the shape of the normal parathyroid gland; when larger, it is round and more nodular. Occasionally, especially when located in the mediastinum, it may be attached by a fibrous stalk. Some have had calcified capsules (pl. I–C).

On section, the parenchyma is orange-brown, soft, and in many cases there are small cystic spaces from 0.1 to 1 cm. in diameter, usually filled with clear colorless fluid. These are apparently foci of degeneration; in one case the major part of the tumor was cystic. Rarely, foci of old hemorrhage and fibrous strands are observed (pl. I–B, D).

MICROSCOPIC. In an earlier paper, the adenomas were divided microscopically into many types in the hope that ultimately there might be some correlation with the clinical findings. No correlation was noted in the 19 adenomas described at that time, and none has been discovered in the present much larger group of cases. In retrospect the subdivision was perhaps too fine and some of the types merely represented minor variations in the life cycle of the chief cell. Since it is believed that there is really one type of cell—the chief cell—in the normal parathyroid gland, the water-clear or "wasserhelle" cell being a chief cell with a more vacuolated cytoplasm probably due to hyperfunction, and the oxyphil cell an involuted, nonfunctioning cell, there really is no need to subdivide the adenomas merely on the basis of transitions between these various manifestations of the same type of cell. On the other hand, one should be familiar with the many variations so that the tumor may be recognized as being of parathyroid origin.

PARATHYROID ADENOMA

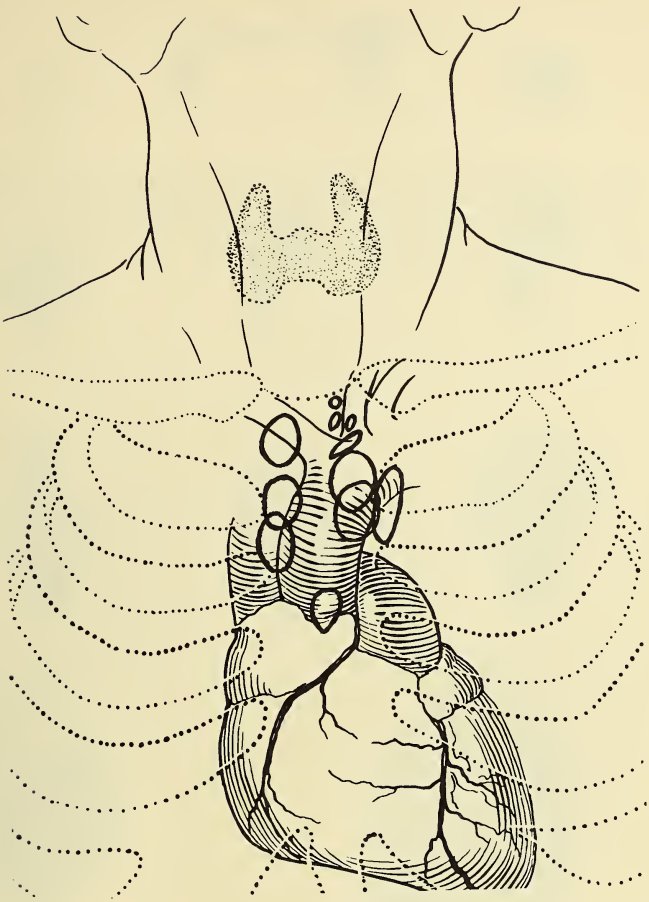


Figure 14. Drawing of the approximate locations and sizes of the first 11 mediastinal parathyroid tumors at the Massachusetts General Hospital. For additional discussion of mediastinal parathyroid tumors, see Mediastinal Parathyroid Adenoma on page 46, Fascicle 18, "Tumors of the Mediastinum." (Figure 2 from Cope, O. Surgery of hyperparathyroidism: the occurrence of parathyroids in the anterior mediastinum and the division of the operation into two stages. Ann. Surg., 114: 706–733, 1941.) A. F. I. P. Acc. No. 218954–81.

PARATHYROID ADENOMA

Figure 15. Actual size drawing of the first 11 tumors removed at the Massachusetts General Hospital. Note the variability in size and shape as well as their encapsulation. Case 1 weighed over 50 gm., while case 2 weighed less than 0.1 gm. (Figure14 from Castleman, B., and Mallory, T. B. The pathology of the parathyroid gland in hyperparathyroidism. A study of 25 cases. Am. J. Path., 11: 1–72, 1935.) A. F. I. P. Acc. No. 218954–82.

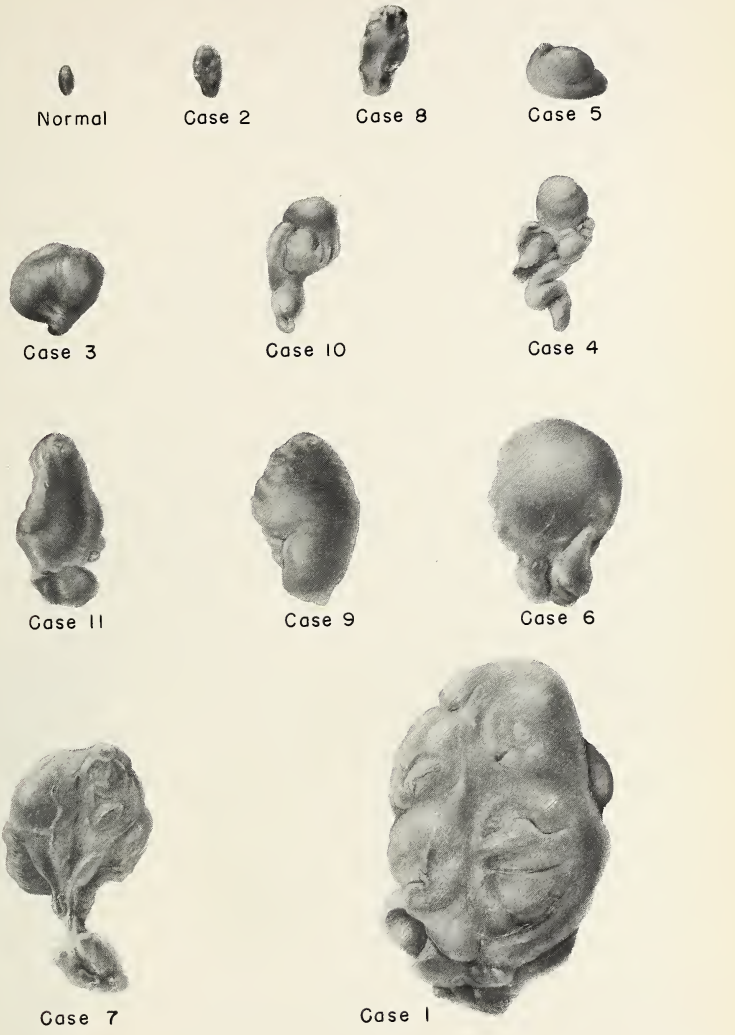

Normal
Case 2
Case 8
Case 5
Case 3
Case 10
Case 4
Case 11
Case 9
Case 6
Case 7
Case 1
E. Glidden '33

Figure 15.

PARATHYROID ADENOMA

Figure 16. Difference in weights of parathyroid adenomas between the classic and nonclassic types of hyperparathyroidism. A. F. I. P. Acc. No. 218954–83.

Figure 17. Difference in the serum calcium values between the classic and nonclassic types of hyperparathyroidism. A. F. I. P. Acc. No. 218954–84.

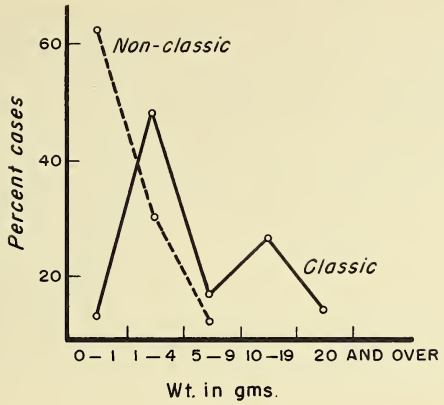

Non-classic
Classic
Percent cases
60
40
20
0—1 1—4 5—9 10—19 20 AND OVER
Wt. in gms.

Fig. 16

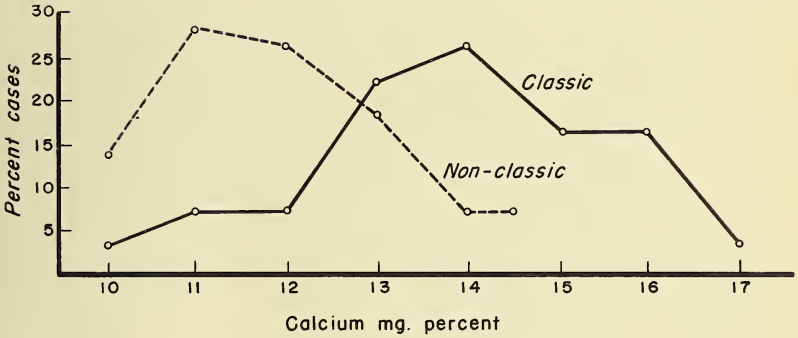

Classic
Non-classic
Percent cases
30
25
20
15
10
5
10 11 12 13 14 15 16 17
Calcium mg. percent

Fig. 17

PARATHYROID ADENOMA

Figure 18. Cross section of entire gland showing a well circumscribed adenoma involving about one half of the gland. × 13. A. F. I. P. Acc. No. 218954–79.

Figure 19. Another example to show a rim of normal parathyroid around an adenoma. Note the abundant fat tissue in the normal gland. × 55. A. F. I. P. Acc. No. 218954–4.

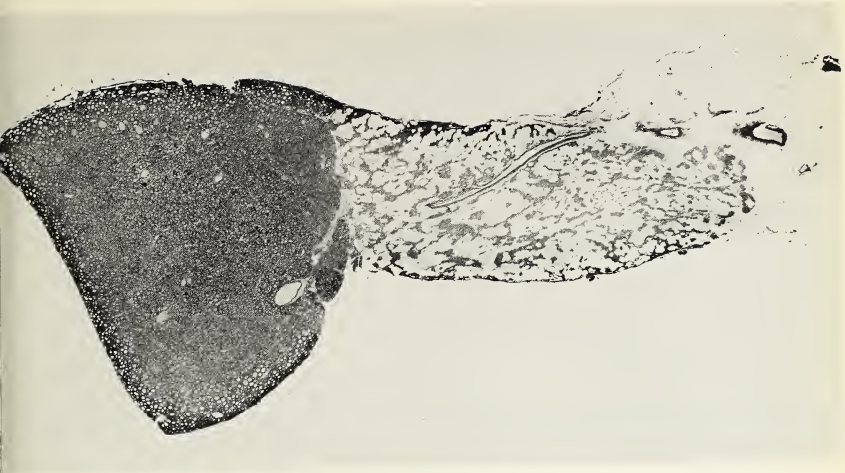


Fig. 18

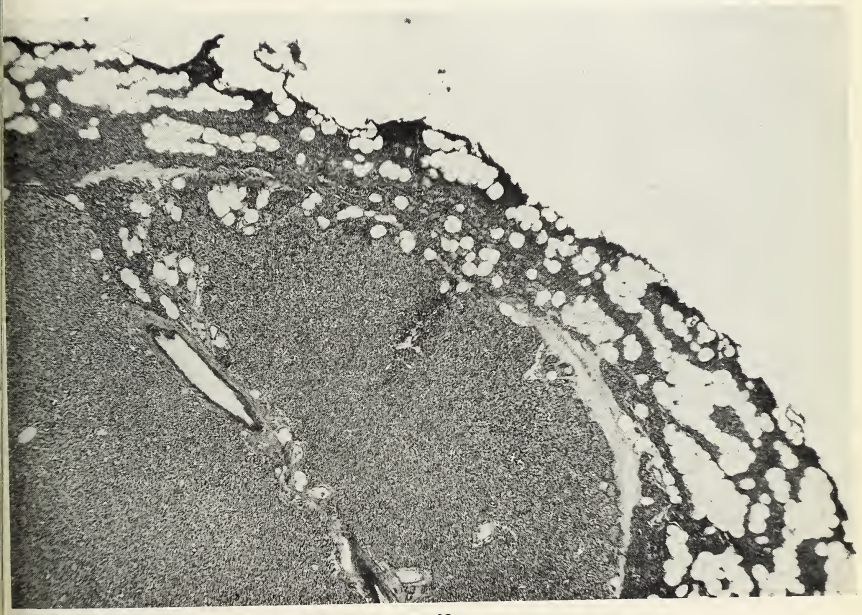


Fig. 19

PARATHYROID ADENOMA

Figure 20. An adenoma composed of normal-sized to slightly enlarged uniform chief cells. Only a rare nucleus is larger than the rest of the cells. Note the compact nature of the tumor and the absence of fat. The cell borders are difficult to make out. × 400. A. F. I. P. Acc. No. 218954–19.

Figure 21. The cytoplasm is vacuolated, accentuating the cell outlines. The cells are larger and several contain two nuclei. This type of vacuolization may be focal or generalized. When generalized, the cells do not reach the size of those seen in primary hyperplasia and hypertrophy. × 400. A. F. I. P. Acc. No. 218954–28.

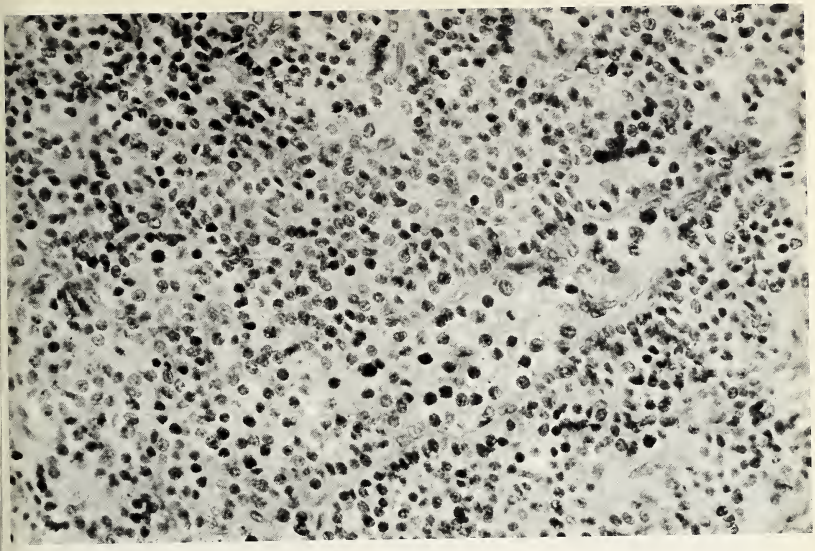


Fig. 20

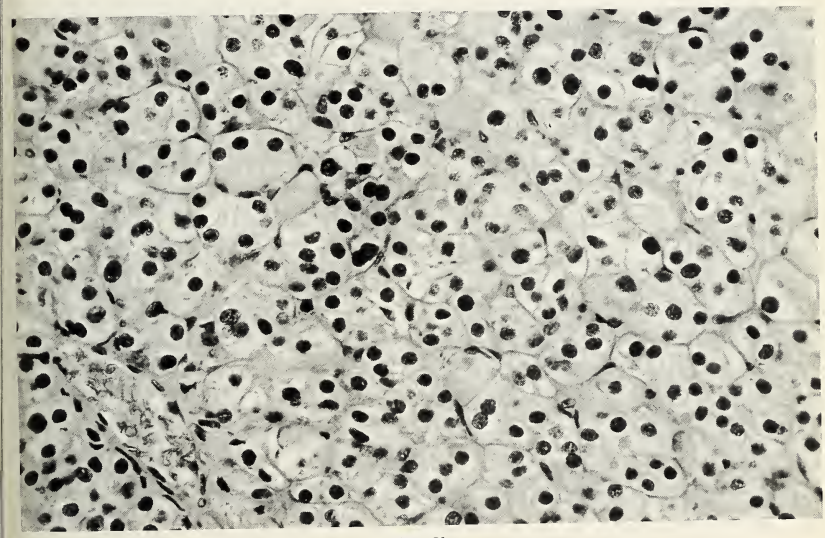


Fig. 21

The cell comprising the bulk of the adenomas is an enlarged chief cell, measuring from 8 to 14 microns in diameter (fig. 20), as compared to the normal measurement of 6 microns. The cell outline is usually not too distinct, although when the cytoplasm becomes vacuolated, the cell outline is more apparent (fig. 21). In hematoxylin-eosin preparations the cytoplasm appears pale pink and granular, occasionally vacuolated (more so after formalin fixation) and only rarely is it deeply acidophilic, like an oxyphil cell (pl. II–A). A functioning true oxyphil adenoma has not been seen in our laboratory. (See also discussion of Oxyphil Adenoma under Nonfunctional Enlargement on p. 74). Although in many cases only one type of cell is present in a given adenoma, very often there is marked variation both as to type and arrangement of cells. Some groups of cells may be vacuolated (fig. 22), others oxyphilic, and they may be arranged as small sharply circumscribed islands (pl. II–C, D). This variability within a tumor is further evidence that the oxyphil and the "wasserhelle" cells are merely transition stages in the activity of the chief cell.

The nucleus of the cells comprising the adenoma is usually large, filling about half the cell, and quite hyperchromatic. Not infrequently the nuclei vary in size within the same tumor; and in about 10 percent of the adenomas, very large hyperchromatic nuclei measuring up to 20 microns are observed (fig. 23). These large nuclei sometimes appear to be a group of smaller nuclei fused into one, simulating the morula stage of embryologic development (fig. 24). Cells with two or three nuclei are very common in the adenomas, but mitoses and anaplasia—usual criteria for malignancy—are not present. One must guard against mistaking a deeply pyknotic irregular nucleus often seen in adenomas for a mitotic figure. The presence of multinucleated cells is a useful criterion in differentiating neoplasia from secondary hyperplasia, where the cells are usually normal in size and contain only one nucleus.

The stroma is usually quite vascular, a finding that is brought out dramatically by the alkaline phosphatase reaction of the endothelium (figs. 25, 26). Although most of the adenomas are fairly solid and are arranged as large islands or broad bands of contiguous cells, in many instances the cells are arranged around a blood vessel in pseudoglandular formation and also at times seem to be forming real acini (figs. 27, 28).

The lining of the glandular space in many cases is composed of high columnar epithelial cells that are extremely vacuolated with basally located nuclei. This pattern may simulate primary hyperplasia and hypertrophy (to be described below), but the individual cells in the latter condition are larger and polyhedral rather than cylindrical (fig. 29).

Since cystic degeneration is common, cysts lined with a single layer of cells and filled with thin granular-staining fluid are often seen (figs. 30–32). This material may simulate the colloid of thyroid tissue, but is usually less dense and

PARATHYROID ADENOMA

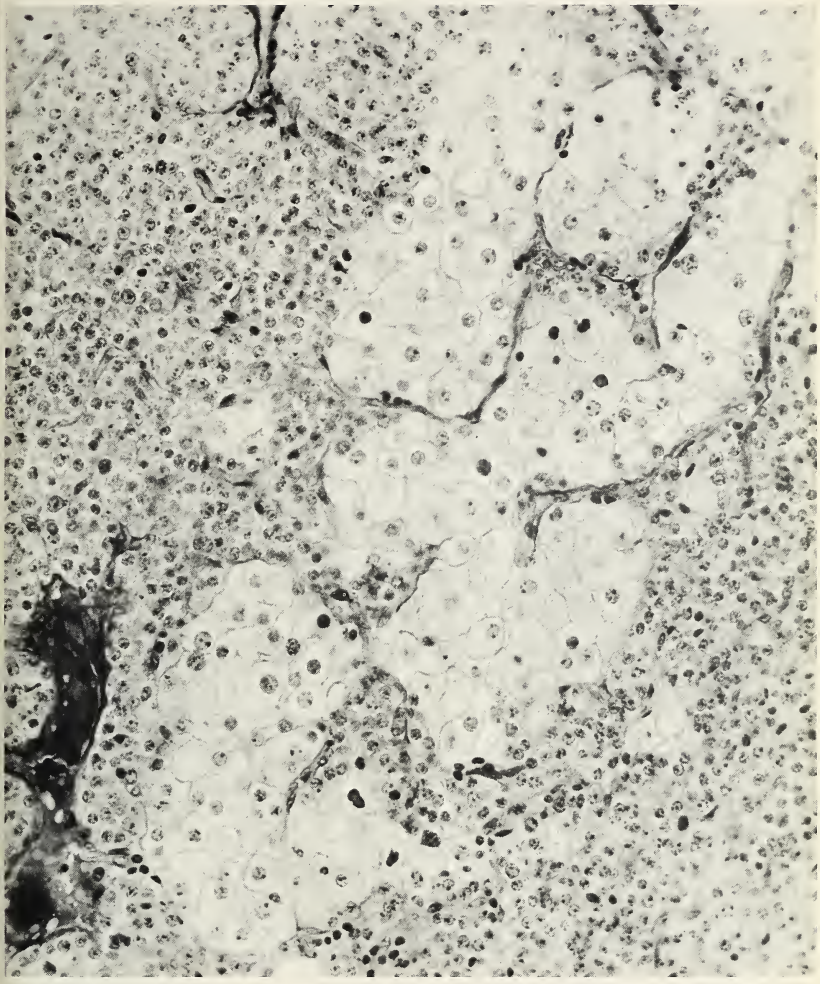


Figure 22. An example of focal vacuolization. Here the cells are as big as those in primary hyperplasia and hypertrophy. Note the surrounding compact chief cells similar to those seen in figure 20. × 400. A. F. I. P. Acc. No. 218954–6.

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Figure 23. An example of the giant nuclei occasionally seen in adenomas. Note the absence of mitoses. These giant nuclei do not connote malignancy. × 400. A. F. I. P. Acc. No. 218954–23.

Figure 24. A higher power of some of the giant nuclei. × 1425. A. F. I. P. Acc. No. 218954–27.

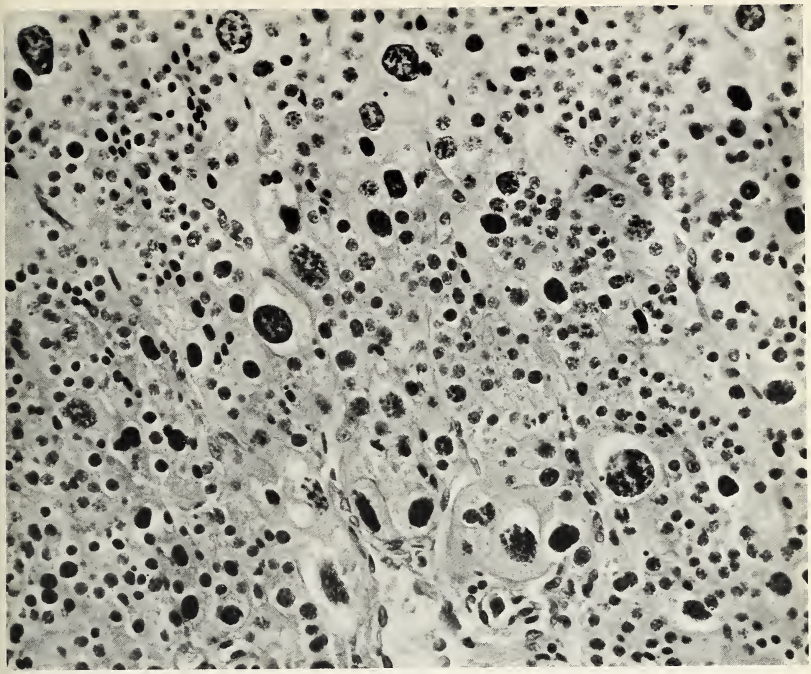

Fig. 23

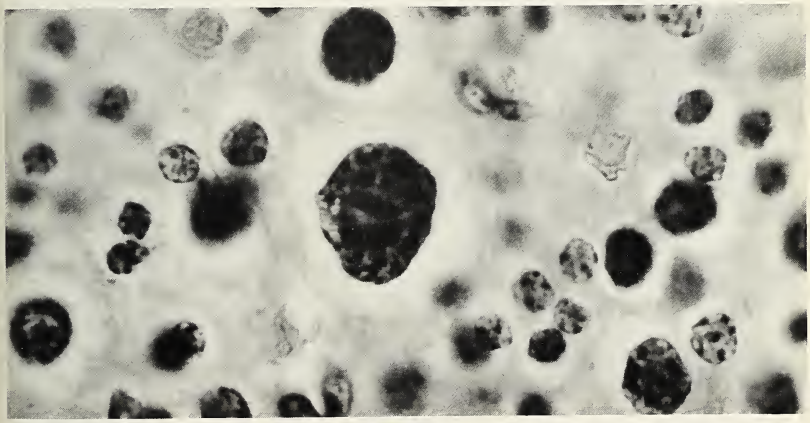

Fig. 24

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Figure 25. Alkaline phosphatase stain demonstrating the extreme vascularity of the tumor. A. F. I. P. Acc. No. 218954–85.

Figure 26. A higher magnification of the preceding figure showing the endothelium stained black with alkaline phosphatase. A. F. I. P. Acc. No. 218954–86.

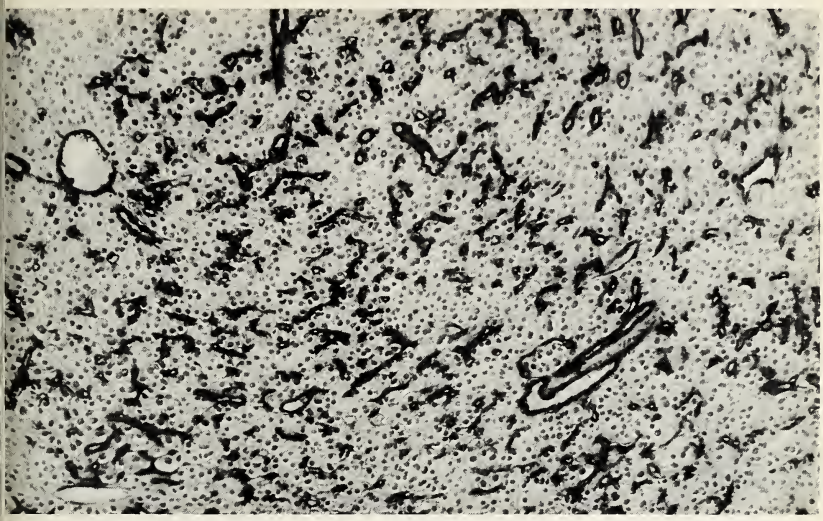

Fig. 25

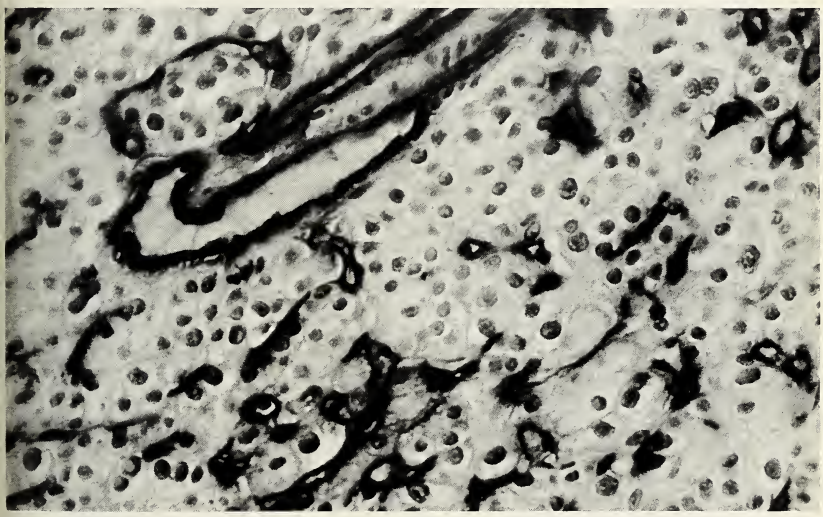

Fig. 26

PARATHYROID ADENOMA

Figure 27. An example of true acinar arrangement. × 90. A. F. I. P. Acc. No. 218954–7.

Figure 28. A higher power of the previous figure. Note the uniform small size of the cells and the amorphous material in the acini. × 400. A. F. I. P. Acc. No. 218954–8.

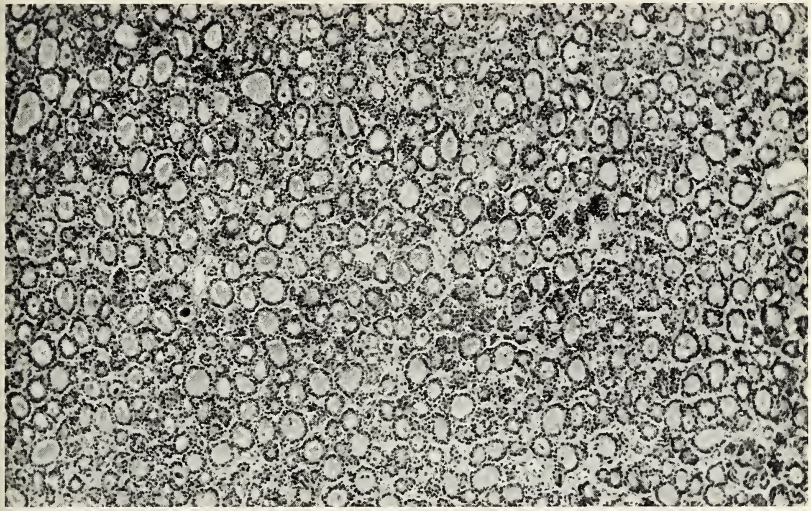

Fig. 27

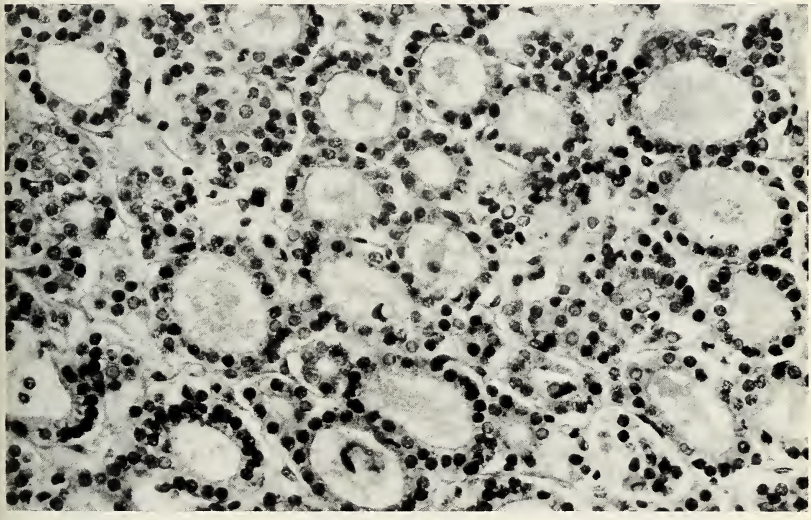

Fig. 28

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Figure 29. An example of vacuolated cells in acinar arrangement, somewhat similar to primary hyperplasia and hypertrophy. × 400. A. F. I. P. Acc. No. 218954–30.

Figure 30. An example of cystic dilatation. × 48. A. F. I. P. Acc. No. 218954–24.

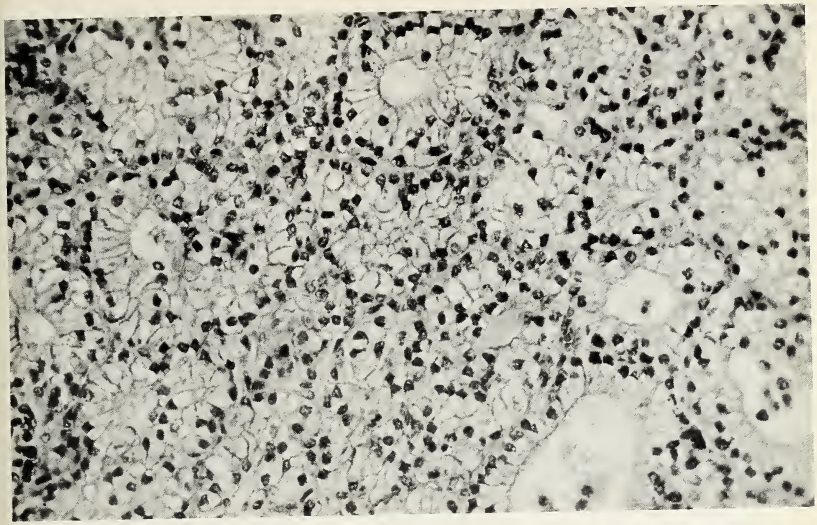


Fig. 29

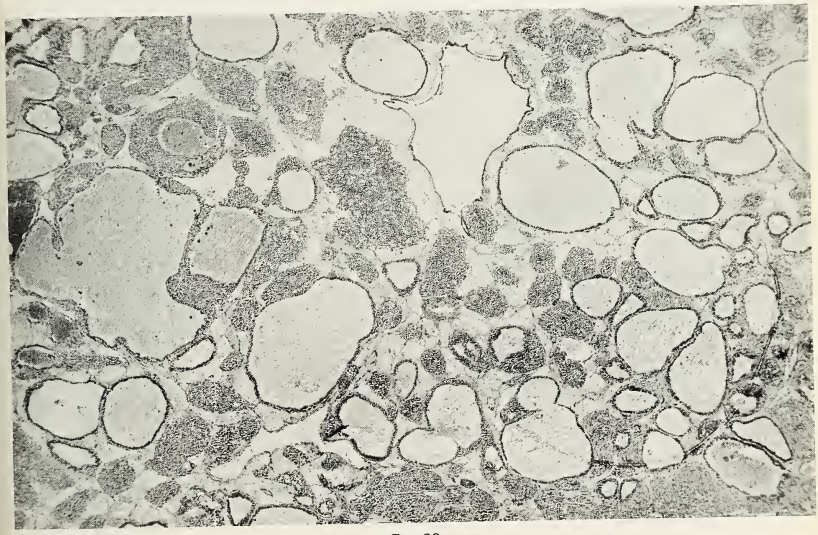


Fig. 30

PARATHYROID ADENOMA

Figure 31. A low power photomicrograph showing early focal cystic degeneration. × 28. A. F. I. P. Acc. No. 218954-65.

Figure 32. A higher power of preceding figure showing a few remaining cells of the parathyroid adenoma in the degenerated area. × 275. A. F. I. P. Acc. No. 218954-12.

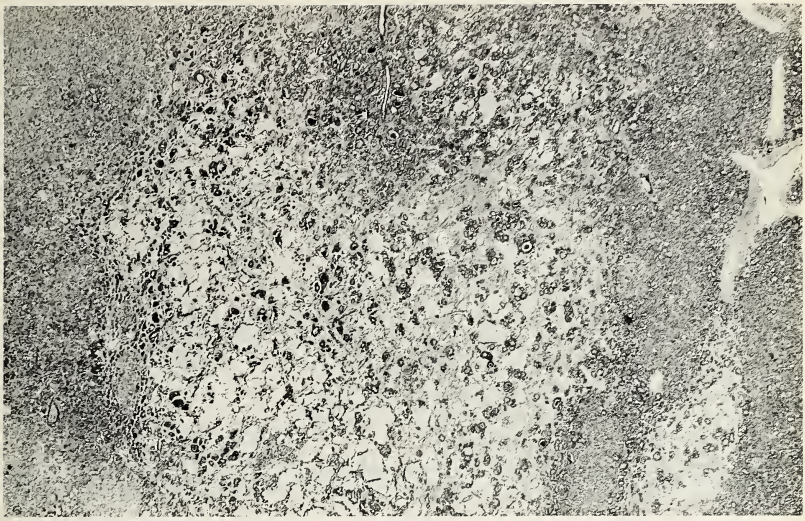


Fig. 31

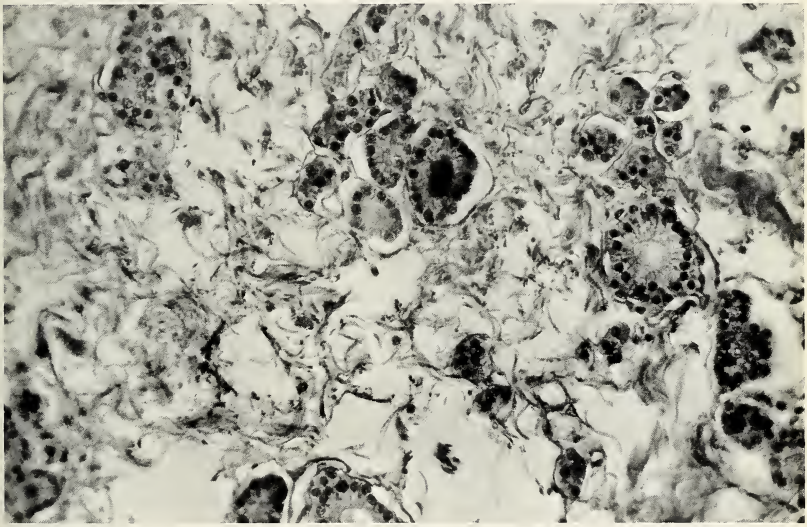


Fig. 32

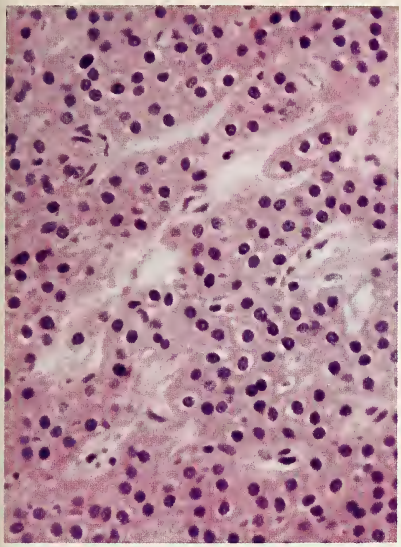
Plate 11. Parathyroid Adenomas

A. An adenoma with cytoplasm more eosinophilic than usual but not as deeply stained as the true oxyphil cell. This was previously called "transitional oxyphil-cell type." × 400. A. F. I. P. Acc. No. 218954–11.

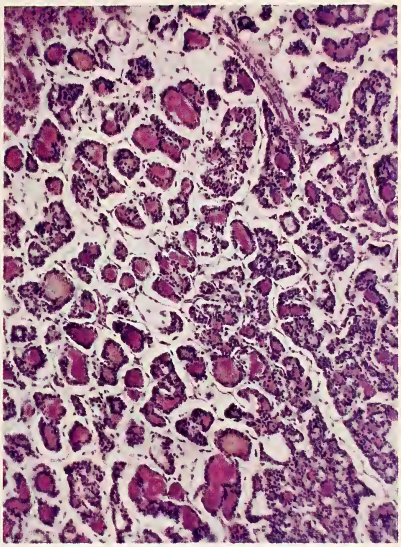
B. An example of the colloid-like material within acini, showing resemblance to thyroid. A. F. I. P. Acc. No. 218954–13.

C. An example of foci of oxyphil cells in an adenoma. × 76. A. F. I. P. Acc. No. 218954–14.

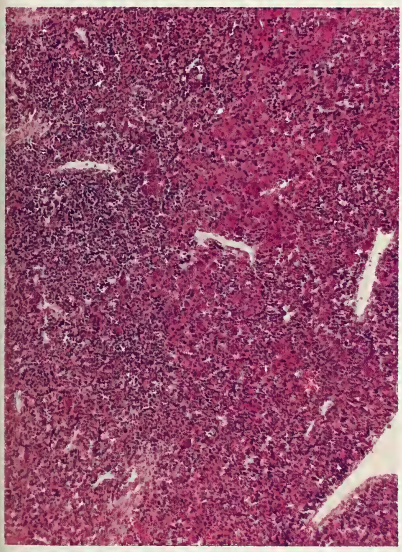
D. A higher magnification of the previous figure. × 400. A. F. I. P. Acc. No. 218954–20.



A



B



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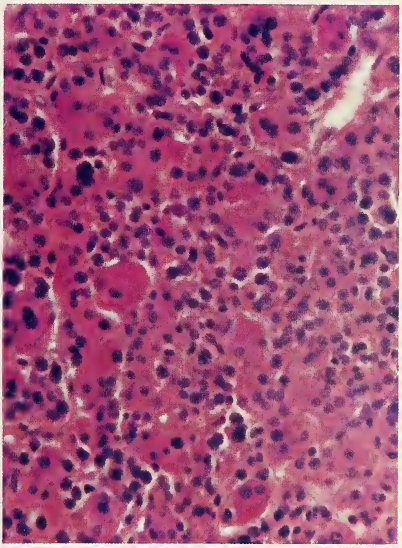

D

Plate II

PARATHYROID ADENOMA

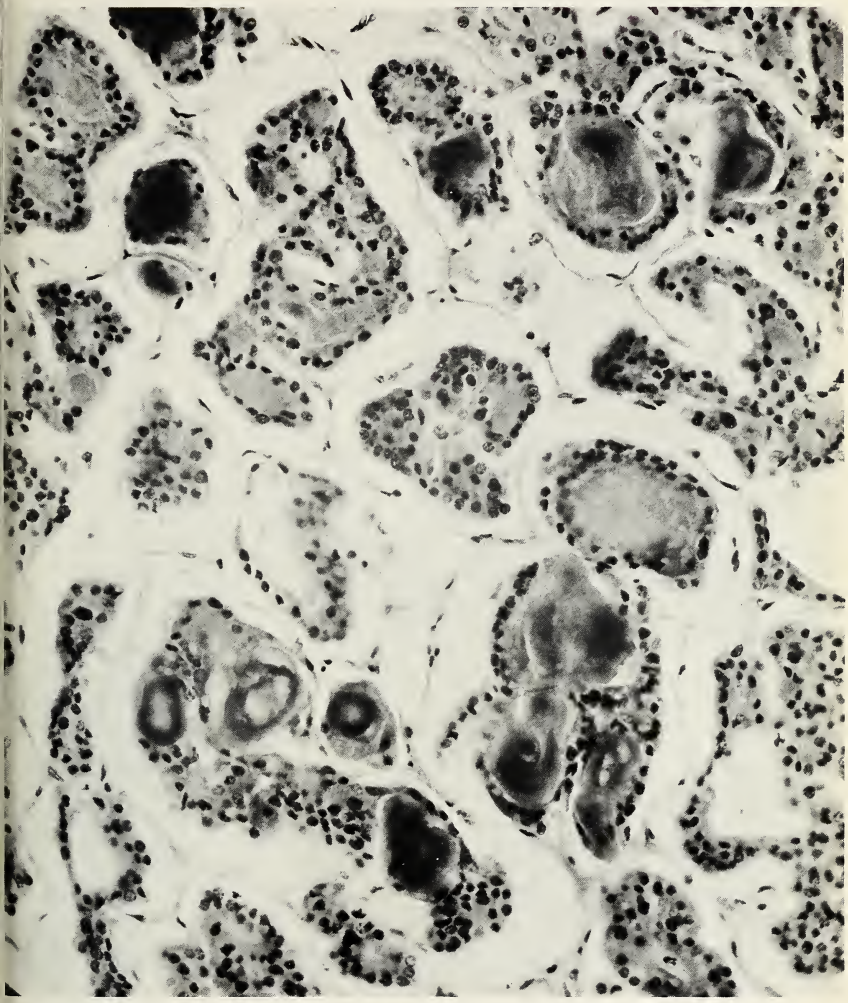

Figure 33. A higher magnification of the colloid-like filled acini shown in plate II–B. × 400. A. F. I. P. Acc. No. 218954–20.

more in keeping with fluid. Occasionally one may have difficulty in deciding whether a lesion is of thyroid or parathyroid origin, and it is important to bear in mind that colloid-like material and acini may be seen in the parathyroid adenoma (pl. II–B, fig. 33).

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Carcinoma

A very rare but definite cause of hyperparathyroidism is primary carcinoma of the parathyroid gland. In the Massachusetts General Hospital series of 100 cases, it occurred 3 times. In addition to these 3 cases (not included by Norris), the author has personally examined the material of 5 other cases sent to the laboratory, 4 of which are included in Norris' paper. According to Norris, who was able to collect 15 cases, it occurred in about 3 percent of all the parathyroid tumors reported in the literature. However, in 8 of these cases there were no chemical or clinical data to confirm the histologic evidence that these tumors were of parthyroid origin. Although it is true that tumors of endocrine glands may be functionless, the similarity of the parathyroid carcinoma to thyroid tumors is often so great that it may perhaps be safer to limit our discussion of parathyroid carcinomas to those that are endocrinologically active, admitting, however, that nonfunctioning parathyroid carcinomas probably do occur.

Black and Ackerman in a recent study of parathyroid tumors go even further in restricting the cases of carcinoma to those with local invasion initially or with distant metastases. They believe that local recurrence is usually due to spillage of cells from an adenoma. Although this latter statement may be true if an obvious adenoma is left in the operative field, it is interesting to note that of the six cases of adenoma in which a subtotal resection was performed (at one time it was believed that postoperative tetany would be prevented or decreased in the patients with severe bone disease if a small portion of the adenoma was left in situ), three had no further evidence of hyperparathyroidism; and in the three that did, there was not much, if any, further growth of the

residuum when removed 5 months, 7 years, and 15 years later. I believe that most recurrences are due to the original invasiveness of the tumor, which in turn is dependent upon its carcinomatous nature.

Since the number of cases of carcinoma is so small, figures as to the sex and age distribution, the location, and the size of the tumors are not statistically significant. One can say, however, that usually the carcinomas are larger than the adenomas and, unlike the adenomas, have in many instances been palpated in the neck. All of the accepted functioning carcinomas have been of the classic type, i. e., with well marked bone disease.

The one clue at operation by which the surgeon knows he is dealing with a carcinoma and not an adenoma is the finding of interadherence between the tumor and the surrounding structures. Unlike the adenoma, which is usually embedded in fat and easily dissected, the carcinoma tends to invade locally; for example, in one of our cases, the surgeon was forced to dissect the tumor away from the esophagus, whose wall it had invaded. This, of course, means that the tumor has invaded and penetrated its capsule, a finding not infrequently observed microscopically and one that has its analogy in thyroid tumors. This same fact also explains the tendency for recurrences to develop locally. Because these tumors are slow-growing, the recurrences are usually late. We have recently seen the material sent to us from Switzerland from a classic case of hyperparathyroidism in which the parathyroid tumor removed was called an adenoma. The signs and symptoms of the disease disappeared only to reappear four years later. A second operation disclosed a recurrence of the tumor. The patient continued to have clinical evidence of hyperparathyroidism, and, following a third exploration, died of a pulmonary embolus. Autopsy showed metastatic disease in the regional lymph nodes and in the liver. I believe this is the first reported case of a liver metastasis from a functioning carcinoma of the parathyroid (fig. 38). Microscopic examination of the slide of the original tumor showed carcinoma. A second case with lung and liver metastases has recently been reported by Ellis and Barr.

The route of metastasis is first to the regional lymph nodes, and for that reason, once the diagnosis is established, a radical neck resection should be advised. It is important to bear in mind, however, that carcinoma of the parathyroid is exceedingly rare, and one should be very sure of the diagnosis before recommending this treatment. If there is any doubt, it is perhaps wiser to err on the conservative side and follow the patient carefully for chemical evidence of recurrence. Unless metastatic lymph nodes are observed, one should not attempt to make a diagnosis of carcinoma on a rush frozen section at operation.

The microscopic appearance of the carcinoma of the parathyroid differs from that of the adenoma in several respects. In none of the cases personally

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Figure 34. The trabecular pattern often present in the carcinomas is well demonstrated. × 114. A. F. I. P. Acc. No. 218954–31.

Figure 35. Although the cells are fairly uniform, note the tendency to spindle shape and the presence of a mitosis. × 400. A. F. I. P. Acc. No. 218954–32.

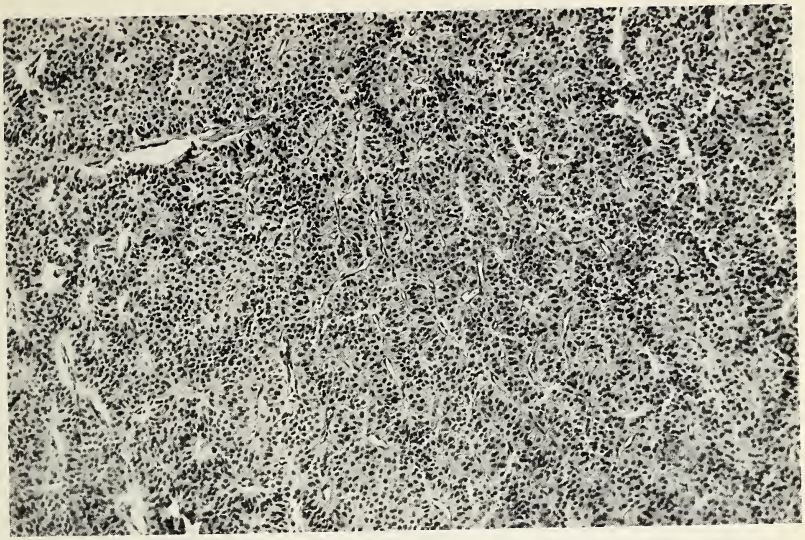

Fig. 34

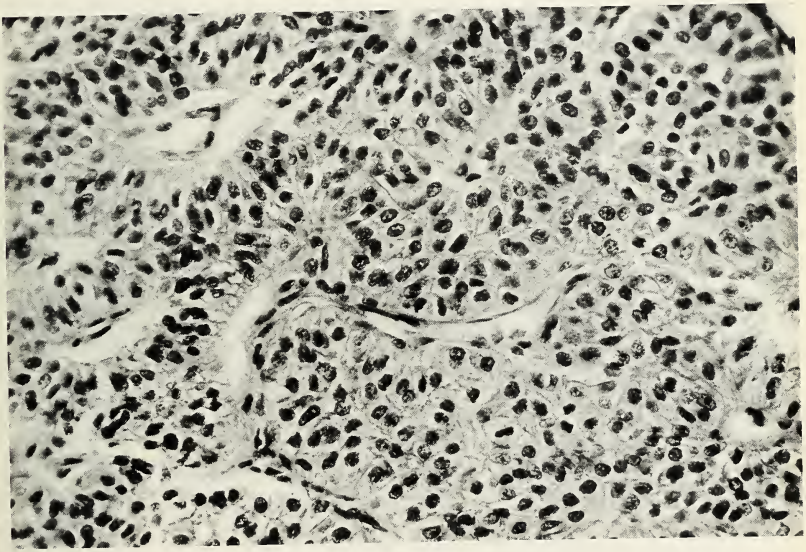

Fig. 35

observed or reported in the literature has there been a rim of normal parathyroid present. Apparently by the time the tumor is observed, it has completly replaced the gland. If enough sections are taken through the capsule, in most cases evidence of capsular invasion will be evident. This in itself, however, is inadequate evidence for a diagnosis of cancer. A not infrequent finding is the extension of the capsular fibrous tissue into the substance of the tumor as irregular dense acellular connective tissue septa (fig. 39). The tumor cells are contiguous with and occasionally invade these septa. Although the arrangement of the cells is just as variable as in the adenomas, in cancer there is a great tendency to trabecular arrangement, which is often exaggerated by the cylindrical shape of the cells (figs. 34, 35). Thus a low power view of a very solid trabecular tumor might be the first clue that one is dealing with carcinoma. The individual cells and nuclei are usually larger than those in the adenomas and atypical nuclei are more numerous. As has been shown above in the section Adenoma, on page 24, nuclear hyperchromatism or even the presence of giant nuclei may not always denote cancer, nor do these characteristics preclude such a diagnosis. In fact, none of the cases of carcinoma showed the large numbers of multinucleated and giant nuclei that are observed in some of the adenomas. Mitoses, which are absent in the adenoma, are always present in the carcinoma (fig. 36). Occasionally they may be hard to find, but I have personally observed them in all eight cases studied (fig. 37). In a few cases they were quite numerous.

In one case there was evidence that an adenoma antedated the development of carcinoma, since parts of the tumor were composed of much smaller uniform chief cells than the large atypical obviously carcinomatous cells (fig. 40). In addition, the capsule of this tumor was very thick, fibrous, and calcified, suggesting a long duration. Clinically, this patient had had symptoms for about 12 years. Many of the other cases of carcinoma also had long histories. Whether all cases of carcinoma develop in pre-existing adenomas would be very difficult to determine.

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PARATHYROID CARCINOMA

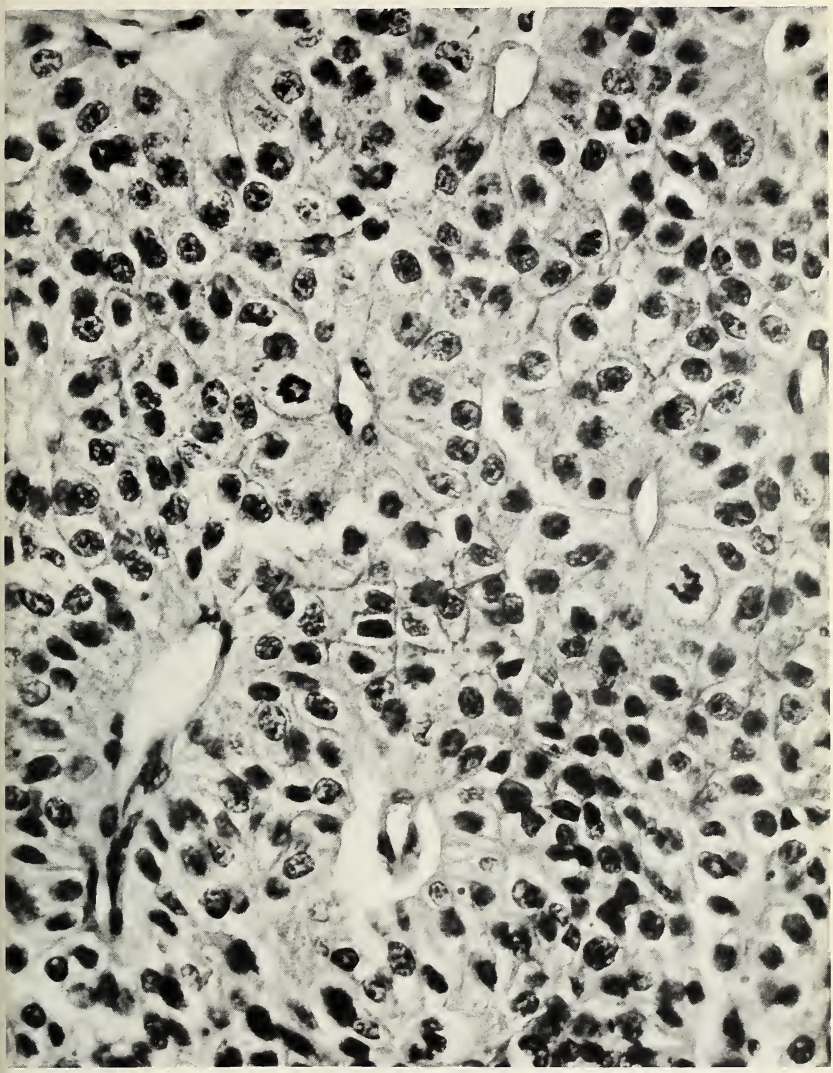

Figure 36. A higher magnification of figure 35 showing uniformity of the carcinoma cells. Note how tumor cells extend to wall of capillary. Two mitoses are present. × 765. A. F. I. P. Acc. No. 218954–33.

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Figure 37. Another case in which the cells are not unlike that of an adenoma, except for the increased size and mitoses. A. F. I. P. Acc. No. 218954–66.

Figure 38. Metastatic nodule in liver. Note persistence of trabecular pattern in metastasis. × 50, further enlarged two diameters. (Permission to reproduce this microscopic slide was granted by Dr. A. von Albertini and Dr. Fritz Koller of Zurich, Switzerland.) A. F. I. P. Acc. No. 218954–35B.

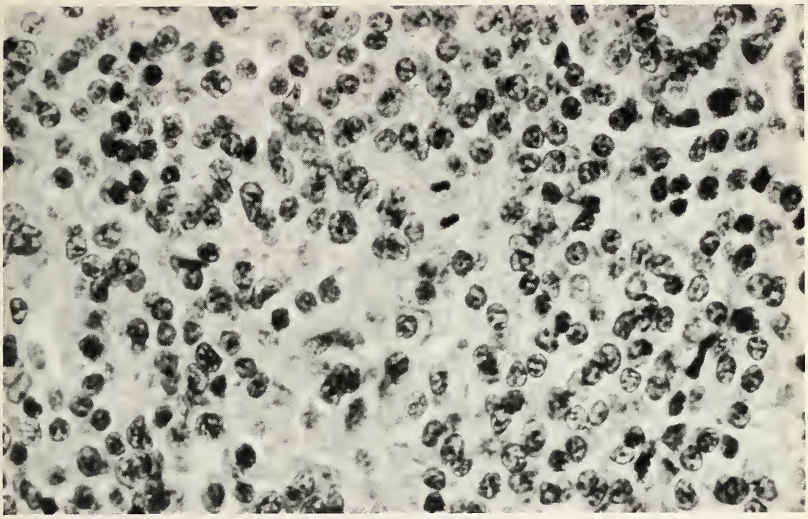

Fig. 37

Fig. 38

PARATHYROID CARCINOMA

Figure 39. Capsular fibrous tissue extending into tumor—a not infrequent finding in carcinoma. × 48. A. F. I. P. Acc. No. 218954–37.

Figure 40. Carcinoma probably arising in a previous adenoma. Note difference in size, shape, and arrangement between the adenoma and the larger carcinoma cells. × 260. A. F. I. P. Acc. No. 218954–68.

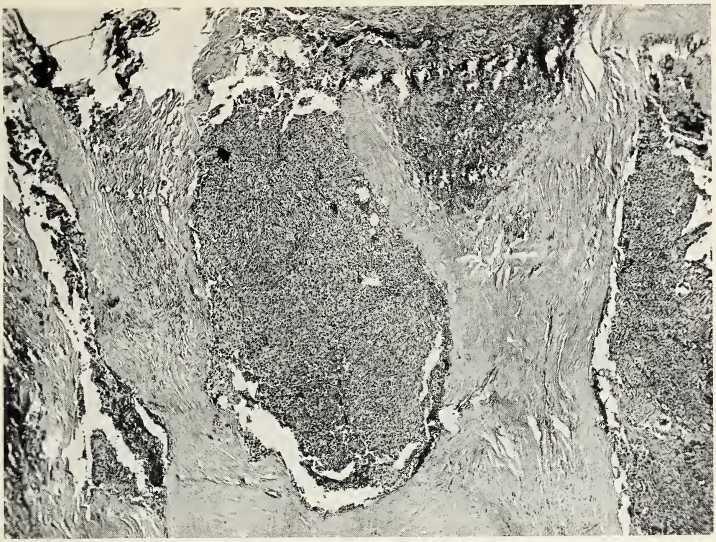

Fig. 39

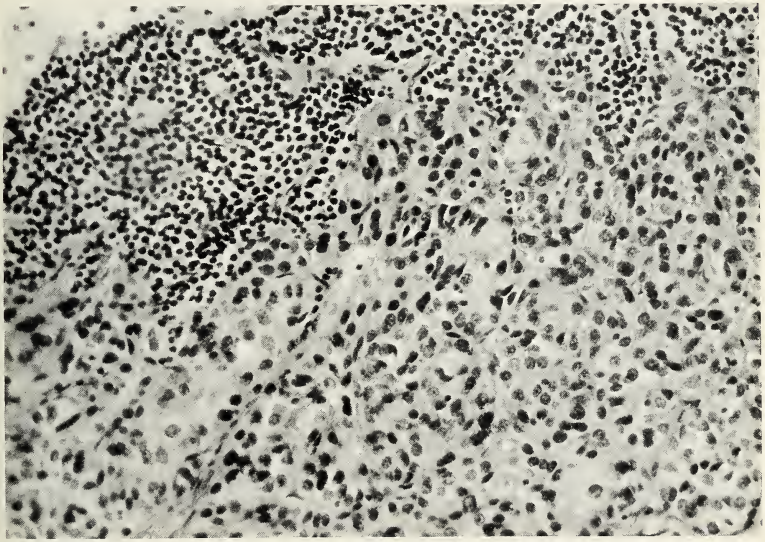

Fig. 40

Primary Hyperplasia and Hypertrophy

In addition to adenoma and carcinoma, which usually involve only one gland, primary hyperparathyroidism may be produced by an enlargement of all the parathyroid glands. One might question the use of the term "primary," since ordinarily when an organ composed of more than one unit is uniformly affected, one thinks in terms of a secondary process produced by a primary stimulus elsewhere. This is true for the parathyroid glands in cases of chronic renal insufficiency where the parathyroid tissue shows secondary hyperplasia, a condition associated with secondary hyperparathyroidism. This section, however, deals with a diffuse enlargement of the parathyroid glands apparently associated with primary hyperparathyroidism, since no other primary cause has as yet been discovered. Originally, this condition was called primary hyperplasia in contrast to secondary hyperplasia (to be described next), which has a very different morphologic picture. Until recently, however, Albright felt very strongly that there was really no increase in the number of cells but merely extreme hypertrophy, and therefore preferred to call this lesion primary hypertrophy. Rogers and Keating, by a series of measurements of cell size and cell volume, concluded that hypertrophy alone would not account for the large size of the glands and introduced the term primary hyperplasia and hypertrophy. This term, I believe (and Albright now concurs), best describes the condition, at least until more is learned about its etiology.

We have had 10 cases of this type, 8 being in our first series of 100 cases of hyperparathyroidism. Clinically, these patients have all revealed renal stones and their presenting symptom was usually produced by the nephrolithiasis. Most of these patients have no evidence of bone disease; in the three that did show only mild decalcification, the alkaline phosphatase ranged between 5 and 7.5 Bodansky units (normal, 2 to 4.5). This is in sharp contrast to the classic adenoma cases with bone involvement where the alkaline phosphatase ranged from 8 to 37 Bodansky units.

GROSS. The appearance of primary hyperplasia and hypertrophy is usually quite different from that of the adenoma. Although encapsulated like the adenoma, the gland of primary hyperplasia and hypertrophy is usually irregular in shape with indentations and pseudopod projections. The glands are soft, pliable, and dark brown, often a mahogany brown (pl. III). (The adenoma is a much lighter brown.) They often contain varying-sized cysts filled with clear fluid. The size and weight of the glands vary a great deal among cases and also within the same case. The total weight of the parathyroid glands in an individual case has been as little as 2 gm., and Paul has reported a case in which two glands weighed a total of 70 gm. An interesting observation among our own cases was the fact that the upper glands were usually much more enlarged than the lower ones. Each of the lower glands usually weighed

PRIMARY PARATHYROID HYPERPLASIA AND HYPERTROPHY

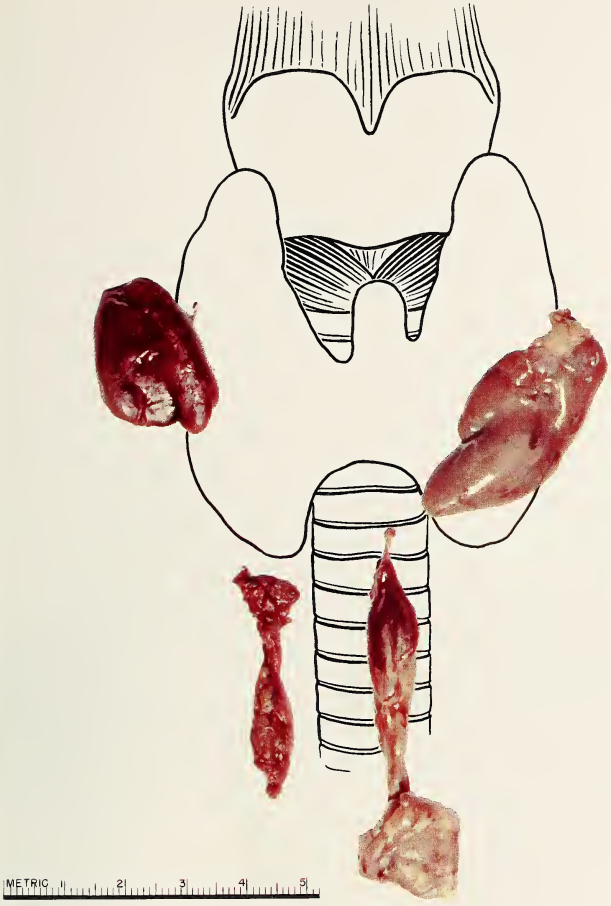

Plate III. Primary hyperplasia and hypertrophy. The upper glands are very much larger than the lower glands. The right lower is embedded in thymic tissue. Note the pseudopod shape of the upper glands and the characteristic brown color. (This is used as a black and white illustration in figure 4 from Castleman, B., and Cope, O. Primary parathyroid hypertrophy and hyperplasia. A review of 11 cases at the Massachusetts General Hospital. Bull. Hosp. Joint Dis., 12: 368–378, 1951.) A. F. I. P. Acc. No. 218954–95.

between 0.1 and 1 gm., while the upper glands weighed between 3 and 30 gm. (figs. 41, 42). This extreme disproportion between upper and lower glands is difficult to explain, especially since it has been shown that the upper glands are, normally, smaller in size than the lower glands. In most of the reported cases the same extreme disproportion between the upper and lower glands was recorded, but since these were usually single case reports, this fact was not commented upon. In fact, it was only when our 10 cases were reviewed in a group, in preparation for this fascicle, that this observation was made. Since the surgical treatment consists in removing all of the parathyroid tissue except a piece equal to about twice the size of a normal gland, removal of only the two upper glands may, if the lower ones are not easily discovered, be sufficient to control the hyperparathyroidism. This may also account for the fact that in some of the reported cases only the upper glands were found, the lower ones being too small to be discovered.

MICROSCOPIC. The most characteristic feature of this condition is the microscopic appearance (figs. 43–46). The capsule is thin and no normal parathyroid tissue is found within or outside of it. There is only one type of cell throughout, the water clear cell, which is polyhedral in shape, sharply demarcated by a thin eosinophilic membrane, and varies from 10 to 40 microns in diameter, averaging 15 to 20 microns. Many of the cell boundaries are broken, with resultant fusion. In contrast to the marked variation in the size of the cell, the nuclei, though often multiple, are all approximately the same size, averaging about 8 microns in diameter. They are round to slightly ovoid, sharply outlined, moderately hyperchromatic; an occasional nucleus is very large and hyperchromatic, similar to the large giant nuclei seen in some of the adenomas. Cytoplasm is clear except that it contains a little light pink-staining granular material. Many of these tiny granules are glycogen deposits. Similar granules are present within the nuclei. There is no intracellular fat although rarely a fat droplet may be found in the stroma. No oxyphil cells are found, and there are no mitoses. The low power appearance is so similar to that of the hypernephroma (renal cell adenocarcinoma) that differentiation would be difficult if the source were not known.

In almost every case there is some variation in the arrangement of the cells. In one area, the cells may be in solid sheets, the nucleus being located in the center of the cell (fig. 46). In an adjacent area, the cells may be a little smaller with the nucleus oriented in the base of the cell, producing a pattern which resembles branches of berries (fig. 43). In a third portion of the gland, the arrangement may be acinar; and in almost every case there is some degree of degeneration with the formation of both microscopic and macroscopic cysts lined with a single row of clear cells (figs. 44, 45). The lumen is often filled with fluid and desquamated cells. Recognition of this variation in pattern, which was emphasized by Rogers and Keating, may be very helpful in a rush frozen sec-

PRIMARY PARATHYROID HYPERPLASIA AND HYPERTROPHY

Figures 41 and 42. Two cases emphasizing the disproportion in size between the upper and lower glands. (Our figure 41 is figure 11 in Churchill, E. D., and Cope, O. The surgical treatment of hyperparathyroidism. Based on 30 cases confirmed by operation. Ann. Surg., 104: 9–35, 1936. Our figures 41 and 42 are both reproduced in figure 4 from Castleman, B., and Cope, O. Primary parathyroid hypertrophy and hyperplasia. A review of 11 cases at the Massachusetts General Hospital. Bull. Hosp. Joint Dis., 12: 368–378, 1951.) A. F. I. P. Acc. No. 218954–87–A and 87–B.

Figure 43. The cells are extremely vacuolated and are arranged in acini. Note basal orientation of the nuclei. × 185. A. F. I. P. Acc. No. 218954–45.

Figure 44. Cellular degeneration with formation of large cystic spaces lined with one or more layers of vacuolated cells. × 90. A. F. I. P. Acc. No. 218954–48.

Fig. 41

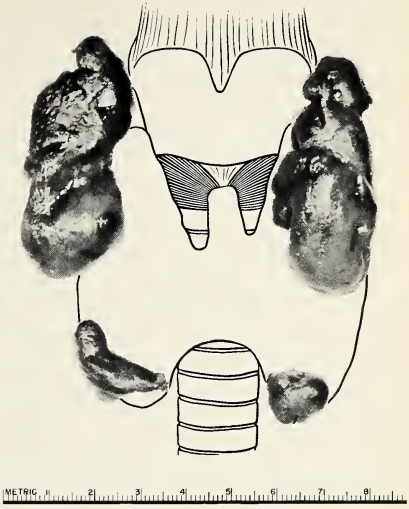

Fig. 42

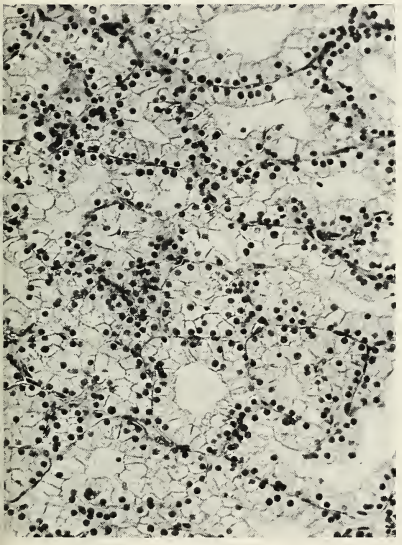

Fig. 43

Fig. 44

PRIMARY PARATHYROID HYPERPLASIA AND HYPERTROPHY

Figure 45. Higher magnification showing similarity to "hypernephroma cell." × 400. A. F. I. P. Acc. No. 218954–46.

Figure 46. From the same gland illustrated in figures 44 and 45. Note the compactness of cells and paucity of glandular arrangement. × 400. A. F. I. P. Acc. No. 218954–47.

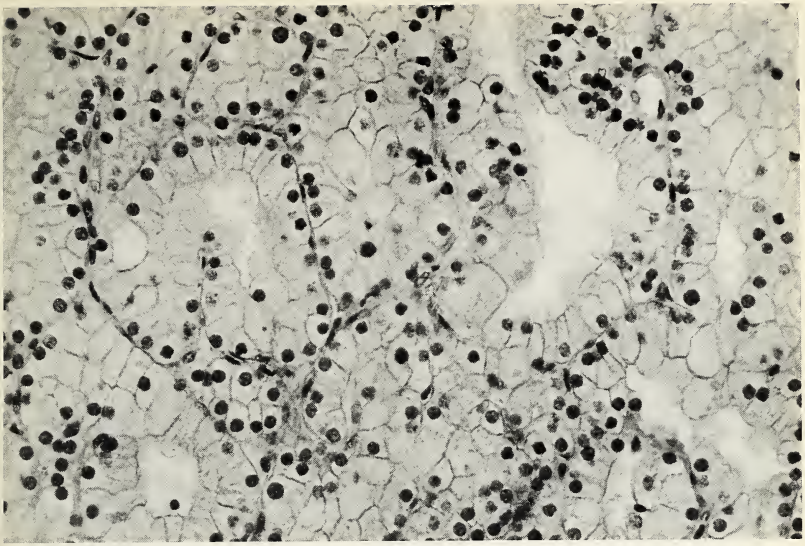

Fig. 45

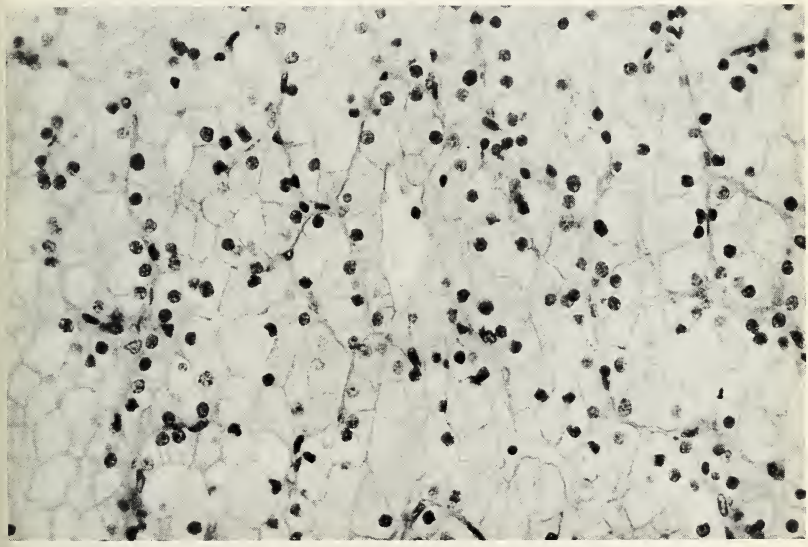

Fig. 46

tion at operation. One must bear in mind, however, that any one of these patterns by itself may be observed in the adenoma.

When the disproportion between the size of the upper and lower glands was recognized as being constant in this condition, microscopic re-examination showed that the cells in the lower glands, although involved in the same process, were occasionally smaller in size than those in the upper glands.

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SECONDARY HYPERPARATHYROIDISM (SECONDARY HYPERPLASIA)

Since secondary hyperplasia of the parathyroid glands may be manifested by gross enlargement, it is important to be able to recognize this lesion so that it may not be mistaken for an adenoma. In most cases, however, the presence of enlargement of all four glands characteristic of hyperplasia, in contrast to the involvement of only one gland or possibly two in adenoma, would make differentiation quite simple.

The most common cause of this condition is chronic renal insufficiency; and the longer the renal impairment, the greater the secondary hyperparathyroidism and the larger the parathyroid glands. The most severe example is so-called "renal rickets" or "renal dwarfism," which is not rickets at all; a better term is renal osteitis fibrosa. (The bone lesions are about the same as those seen in primary hyperparathyroidism although occasionally osteoid seams are seen in secondary hyperplasia.) Ordinary rickets will produce mild secondary parathyroid hyperplasia, as will diffuse bone replacement diseases such as metastatic carcinoma. It is also possible to have an adenoma of one gland produce sufficient calcium deposits in the kidneys so that even after the adenoma is removed surgically, the irreparable renal damage will in turn produce secondary hyperplasia of the remaining parathyroid glands.

The blood chemical findings are usually the reverse of those seen in primary hyperparathyroidism. Whereas in the latter the serum calcium is high and the phosphorus low, in secondary hyperparathyroidism the serum calcium is somewhat depressed and the phosphorus elevated. The serum phosphatase is elevated if bone lesions are present.

The gross and microscopic appearances of the parathyroid glands in secondary hyperplasia were given in detail in a previous paper,* and the criteria for making this diagnosis were tabulated. With a few additions and modifications, they are as follows:

GROSS (figs. 47, 48):

(A) Size: Characteristically slight to moderate enlargement of all glands rarely reaching the size of the usual adenoma or primary hyperplasia and hypertrophy; however, marked variation is not infrequent in the size of the individual glands of a given case and one or all of them may even be normal in size.

* Castleman B., and Mallory, T. B. Parathyroid hyperplasia in chronic renal insufficiency. Am. J. Path., 13: 553–574, 1937.

(B) Color: The glands tend to be a creamy gray rather than an orange-brown.
(C) Consistency: The glands are firmer and much less pliable than the normal gland, the adenoma, or the glands of primary hyperplasia and hypertrophy.

MICROSCOPIC:

(A) Low Power:
1. Uniformity of all glands in a given case (fig. 49).
2. Absence or marked decrease in intercellular fat cells.
3. Increase in number of cells as shown by widening of the epithelial columns.
4. Development of compact areas in which columnar arrangement is no longer distinguishable.
5. Tendency to acinar arrangement in the more advanced cases.
6. Uniformity of the whole gland except in the more advanced cases where there is a tendency to adenoma-like and papillary formations without real encapsulation (figs. 50, 51).
7. In formalin-fixed tissues, the shrinkage produces a separation of the cells from the walls of the blood vessels and stroma so that a pseudocolumnar acinar, and sometimes papillary arrangement results. Since most of the material in secondary hyperplasia is necropsy rather than surgical, the added postmortem change increases this shrinkage tendency.

(B) High Power:
1. Cells are uniform normal-sized chief cells, unlike the cells in adenoma or primary hyperplasia and hypertrophy.
2. Tendency to vacuolization of the cytoplasm in less severe cases producing slight to moderate cell enlargement, but not reaching the size of the cells in primary hyperplasia and hypertrophy (figs. 52, 53).
3. No mitoses, nor the hyperchromatism, multinucleated cells, and variation in nuclear size which are pathognomonic of the adenoma.
4. Oxyphil cells more numerous than expected for age of individual.
5. Glycogen content slightly higher than in adenoma or primary hyperplasia and hypertrophy.

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SECONDARY PARATHYROID HYPERPLASIA

Figure 47.* Posterior view. Case of adult renal osteitis fibrosa with ectopic calcification showing marked enlargement of all four parathyroid glands. Total weight was approximately 11 gm. A. F. I. P. Acc. No. 218954–88.

Figure 48.* Mild enlargement in case of chronic glomerulonephritis. All four glands are rounded and plump rather than thin and elongated. Their weight was 360 mg. (normal plus or minus 140 mg.). A. F. I. P. Acc. No. 218954–89.

Figure 49. There is an increase in the number of normal-sized chief cells with replacement of fat cells. Note the compactness of the cells and the absence of columnar arrangement. × 400. A. F. I. P. Acc. No. 218954–51.

Figure 50.* A low power photomicrograph showing many circumscribed encapsulated islands of cells. This arrangement is seen only in the more severe grades of hyperplasia in cases with long-standing renal insufficiency (23 years). × 10. A. F. I. P. Acc. No. 218954–90.

*From Castleman, B., and Mallory, T. B. Parathyroid hyperplasia in chronic renal insufficiency. Am. J. Path., 13: 553–574, 1937. Figure 4 is our figure 47, figure 10 is our figure 48, and figures 5 and 6 are our figure 50.

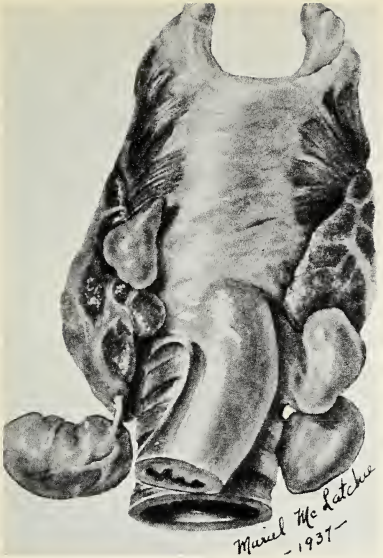

Fig. 47

Fig. 48

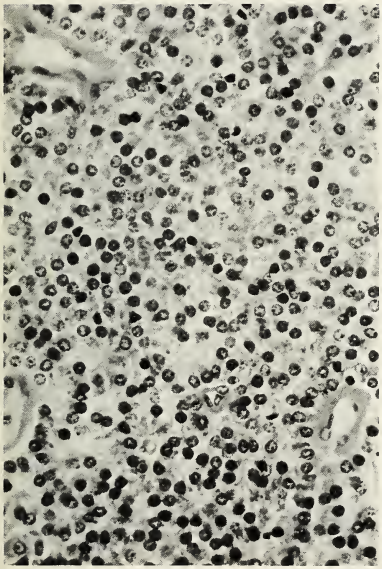

Fig. 49

Fig. 50

SECONDARY PARATHYROID HYPERPLASIA

Figure 51. Another example of the result of long-standing renal insufficiency, showing the early formation of a hyperplastic island of chief cells. × 70. A. F. I. P. Acc. No. 218954–56.

Figure 52. A case of true rickets or osteomalacia showing mild vacuolization of the cytoplasm. × 400. A. F. I. P. Acc. No. 218954–61.

Figure 53. A case of polycystic kidneys with known chronic renal insufficiency for three years, showing slight enlargement of the cells and vacuolization of the cytoplasm. × 400. A. F. I. P. Acc. No. 218954–69.

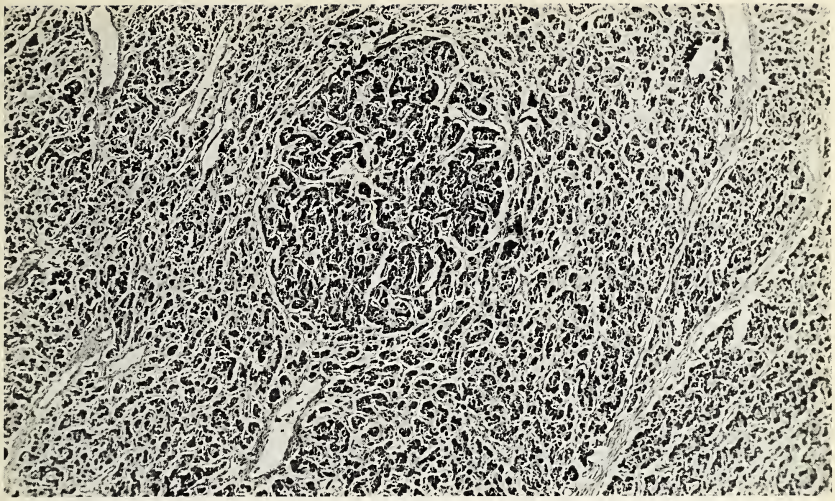

Fig. 51

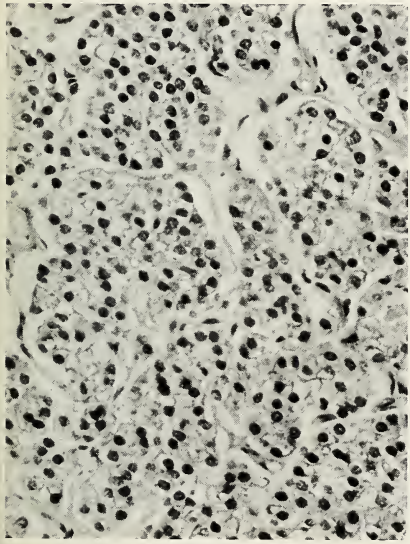

Fig. 52

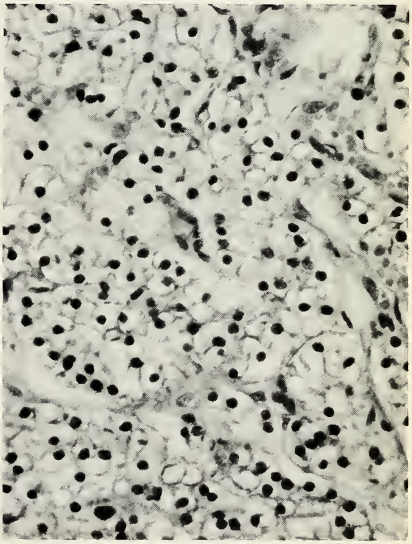

Fig. 53

NONFUNCTIONAL ENLARGEMENT

Oxyphil Adenoma

It is well known that the number of oxyphil cells increases with the age of the individual (see Normal Parathyroid Gland, p. 1). In the older age group, the oxyphil cells are seen in islands, which may attain sufficient size by fusion of many islands to resemble a neoplasm. Since it is believed that the oxyphil cell is an involuted inactive chief cell, one would not expect these oxyphil islands or adenomas to be active. It is quite possible that the oxyphil adenoma may represent a previously active adenoma which has completely involuted, perhaps similar to the so-called Hürthle-cell tumor of the thyroid, which is believed by some to be an involuted fetal adenoma. (See also discussion under Adenoma, p. 24).

Cysts

Cysts of the parathyroid are generally the result of degeneration. They are quite common, both grossly and microscopically, in the active adenoma and in primary hyperplasia and hypertrophy. Not infrequently they are incidental in a normal gland. Cysts large enough to be seen grossly are rare.

Carcinoma

PRIMARY. Primary nonfunctional carcinomas have been reported, but it is very difficult in these cases to be absolutely sure that they are not of thyroid origin (see section on Carcinoma under Primary Hyperparathyroidism). Dr. Fred W. Stewart stated in a personal communication that although he had not actually seen a nonfunctioning primary carcinoma of the parathyroid gland, "the mere fact that throughout the tumor field function is an expression of retained normal physiologic attributes and that in neoplasia the tendency is ever toward increasing loss of such attributes" allows him to "continue to doubt that the parathyroid is an exception to a general rule."

METASTATIC. Metastatic carcinoma not infrequently involves parathyroid tissue in cases of extensive carcinomatosis. An accurate incidence, however, is not available because these glands have not been examined microscopically in a sufficient number of routine necropsies.

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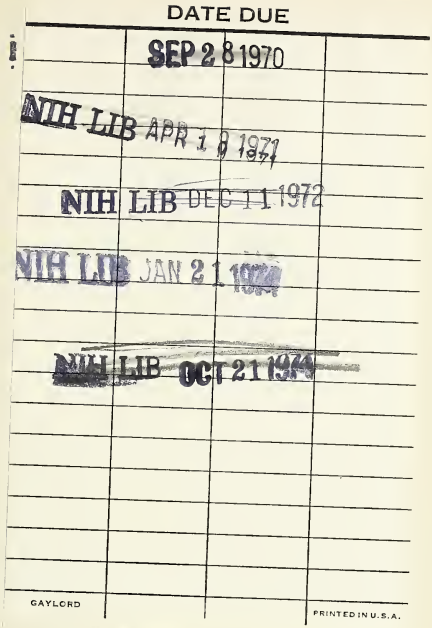

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